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Spatial neglect clinical and neuroscience review: a wealth of information on the poverty of attention

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Abstract

Hemispatial neglect (HSN) is a frequent, conspicuous neurobehavioral accompaniment of brain injury. Patients with HSN share several superficial similarities, leading earlier clinical neuroscientists to view neglect as a unitary condition associated with brain structures that mediate relatively discrete spatial cognitive mechanisms. Over the last two decades, research largely deconstructed the neglect syndrome, revealing a remarkable heterogeneity of behaviors and providing insight into multiple component processes, both spatial and nonspatial, that contribute to hemispatial neglect. This review surveys visual HSN, presenting first the means for detection and diagnosis in its manifold variations. We summarize cognitive operations relevant to spatial attention and evidence for their role in neglect behaviors and then briefly consider neural systems that may subserve the component processes. Finally, we propose several methods for rehabilitating HSN, including the challenges facing remediation of such a heterogeneous cognitive disorder.

Keywords

Neglect, Hemispatial; Spatial attention, orienting, alerting; Rehabilitation

Introduction

Healthy humans ordinarily take full measure of their environment without regard to the spatial location from which information originates. Following brain injury, on the other hand, individuals may demonstrate a spatially circumscribed behavioral deficit of asymmetric attention and action, hemispatial neglect (HSN). Severe, persistent neglect behavior most frequently follows right hemisphere injury, occurring in about half of right hemisphere stroke survivors, and results in contralesional, or left, spatial environmental errors.¹

A popular operational definition of HSN asserts that patients defectively detect, orient or respond to stimuli from spatial regions contralateral to brain lesions.² An important caveat specifies that the deficit not be attributable to malfunction in more basic sensory or motor systems, a requirement that can be clinically challenging to establish.³ While succinct, this description fails to capture how manifestations of disordered spatial attention vary across an immense spectrum. While HSN may affect perception or internal representation in any or multiple sensory modalities, as well as motor planning and execution, the following review

focuses on visuospatial attention for three reasons. First, humans may exhibit an inherent bias towards spatial information in the visual modality.^{4,5} Second, visually-guided behavior may dominate human activities of daily living. Lastly, the majority of human lesion studies of HSN and functional brain imaging research on spatial orienting examine responses to visual stimuli.

As presented herein, spatial neglect comprises a heterogeneous, multifaceted set of behavioral symptoms, a point emphasized universally in recent reviews.^{3,6–9} The range and diversity of neglect-associated deficits presents a substantial obstacle to cognitive theorists attempting to create unifying models of normal spatial cognition. For clinicians, neglect heterogeneity thwarts attempts to identify a single associated lesion location, a universally applicable recovery trajectory, or intervention plan for affected patients.

The following review first considers the most critical source of neglect variability (or subject heterogeneity): the means by which clinicians demonstrate HSN in their patients. Later sections present a summary of how subject heterogeneity in neglect may help inform understanding of neuroanatomic structures with relevance to normal spatial cognition. Lastly, the review introduces how subject heterogeneity may be important for directing patients to more effective management and treatment during recovery.

Recognizing the many faces of HSN

Early after brain injury, signs consistent with HSN can be observed during informal bedside assessment. Patients with severe spatial neglect often show spontaneous ipsilesional deviation of the head and eyes.¹⁰ When addressed from their left side, such patients may actually turn away from the examiner, replying to the right side even when there is no interrogator present in this direction of gaze. Other readily apparent indicators of HSN include ignoring food items on the their plate's contralesional side or failing to locate utensils on their tray's contralateral side. Patients with neglect may also inadvertently strike contralesional obstacles such as door frames or furniture when ambulating or propelling a wheelchair.

Clinicians can also elicit HSN in individuals with milder deficits or at later stages of recovery, using tasks that requiring distribution of perceptual attention and response over both sides of space. Cancellation tasks, a sensitive paper-and-pencil method of neglect assessment, ask patients to detect and indicate targets from an array containing either targets alone or targets embedded amongst a variety of distractors.^{11,12} Other common tests include line bisection and figure copying and drawing from memory.³ Examiners typically present stimuli and evoke responses in a location centered with respect to the patient's eyes, head and trunk. Spatial neglect may manifests as failure to cancel contralesional targets, ipsilesional deviation on line bisection (for relatively long lines), and omissions, errors or distortions of the contralesional aspects of rendered figures (Figure 1). Even when patients mark all targets in a cancellation pattern, observing qualitative features of their performance may reveal persisting spatial bias. Specifically, patients with HSN tend to initiate search and cancellation on the right side, a stark contrast to healthy right-handed subjects who most often begin on the left.¹³ In fact, one large series of right hemisphere stroke patients concluded that the starting mark's position on a specific cancellation task (the Bells Test) was the most sensitive, though not specific, clinical indicator of neglect.^{14,15}

Note that all assessment methods mentioned above require some degree of visuomotor integration and coordination. Spatial neglect can be alternatively tested with tasks entailing no limb motor response. For example, the Wundt-Jastrow illusion consist of two identical shapes whose configuration induces normal individuals to misjudge one figure, extending further to the left, as longer.¹⁶ Patients with HSN experience the opposite illusion, selecting the shape which extends further to the right. Spatial bias can also be demonstrated with the "Landmark test" in which examiners present prebisected lines, marked at varying distances to the left and

right of midpoint, and instruct patients to judge which line end is closer to the mark.¹⁷ Patients with spatial neglect predominantly select the left end, suggesting that they may perceive the leftward line segment as shorter.

Other means of eliciting neglect without limb movements include spatial analysis of reading. Patients with HSN following right brain injury may misread words either through omission or distortion of leftward characters (e.g., “REACTION” read as “ACTION” or “TRACTION”). Alternatively, patients with neglect may fail to read words from the left side of a paragraph or entries from the left half of a menu.^{18,19}

Another frequently associated phenomenon is extinction. Early after injury, patients with HSN may fail to detect contralesional sensory stimuli or, when detected, mislateralize them to the opposite side, a finding termed allesthesia. With recovery, patients improve their ability to detect single visual, auditory or tactile stimuli from the neglected side, but may fail to detect or “extinguish” these contralesional stimuli when presented simultaneously with a comparable ipsilesional stimulus.²⁰ Some investigators assert that, based on clinical and neuroanatomic grounds, extinction should be considered as a completely independent phenomenon from neglect.⁸ Recent psychophysical experiments provide contradictory evidence, however, illustrating how the coarse nature of stimulus properties may undermine conclusions based on clinical double-simultaneous stimulation techniques.²¹

The above tasks primarily evaluate perceptual-attentional and motor-intentional abilities, rather than assessing internal imagery or the “mental representation” of space. Such functions may be selectively impaired in some patients who can satisfactorily describe a known site’s layout (e.g., their apartment’s floorplan), but omit left-sided details.^{22,23} Other means of detecting “imaginal” or representational neglect include assessing map orientation or drawing from memory (Figure 2). For example, examiners can contrast figures rendered from memory to copying the same item: individuals with isolated imaginal neglect may copy figures adequately, but leave out contralesional features when drawing from memory.²⁴ Another recently described test of imaginal neglect asks subjects to determine the midpoint of a “mental number line”, an analogical left-to-right oriented representation of numbers in ascending order.²⁵ When determining which numeral occurs halfway between number pairs of varying intervals, patients with neglect err toward larger numbers (e.g., stating that the number halfway between “six” and “twelve” is “eight”). Analogous to performance on standard line bisection tasks, the magnitude of error varies in proportion to the size of the internumeric interval.²⁶

Because patients may exhibit spatial bias on some tasks but perform normally on others, it has been recommended that batteries to identify spatial neglect and classify its severity should contain a variety of subtests.^{15,27,28} Studies characterizing HSN over the last three decades document a remarkable number of dissociations, literally between every assessment method mentioned above, that suggest the existence of separable spatial neglect subtypes. For example, patients may omit left-sided targets from cancellation arrays while bisecting lines adequately, and vice versa.²⁹ Double dissociations have been also been reported between physical and mental line bisection, extinction of left-sided stimuli and bias on paper-and-pencil tasks, and between representational neglect and performance on a battery of clinical neglect tests, to name but a few.^{30–32} An important issue regarding between-task dissociations relates to whether study designs accounts for fatigue through counterbalancing task order. More importantly, these data refer only to within-subject performance discrepancies between different measures of neglect. However, as reviewed below, the validity of dissociable behavioral features in spatial neglect has been substantiated through observation of within-task dissociations based on reference frame, stage of processing and distance.

The effect of reference frame

Manifestations of HSN may vary as a function of which spatial reference frame determines abnormal responses. Contemporary cognitive models posit that visuospatial processing involves representations anchored in hierarchically abstract coordinates. For example, multiple egocentric reference frames (eye-, head- and trunk-centered) may define spatial coordinates with respect to the viewer. A more abstract allocentric or “stimulus-centered” reference defines an object’s location without regard to viewer perspective. Consider someone looking at a clock. Directly in front of the viewer, numerals 7–11 fall on the left side of both egocentric and allocentric space. After moving the clock rightward away from the viewer’s midline, the same numerals now occupy the right side in a viewer-centered reference frame while their left-sided position in stimulus-centered coordinates remains unaffected. Hillis and others describe an even more abstract “object-centered” reference definable for entities with canonical orientations.³³ At this level of representation, left and right are determined without regard to an object’s orientation or location relative to the viewer (i.e., clock numerals 7–11 are universally left-sided with respect to its top). Experiments that record from individual neurons confirm the neural segregation of different coordinate systems. While activity in some units shows selectivity of responses to a stimulus-centered reference frame, the majority of parietal neurons appear “tuned” to a viewer-centered reference.³⁴

Patients with HSN may demonstrate spatial bias consistent with either or both viewer-centered and stimulus-centered reference frames.^{35–37} In a classical experiment, patients with neglect after right brain injury photographed a ruler with its long axis aligned horizontally.³⁸ Most patients displaced the ruler’s image to the picture’s right side, consistent with their bias on other clinical neglect tests. In contrast, a few individuals displaced the ruler’s image to the picture’s left side. Results suggested that the former group’s spatial bias may respect viewer-centered coordinates, while the latter cases were more influenced by a stimulus-centered reference. Ota and colleagues reported another clever, practical means of evaluating neglect frame of reference.³⁹ Their modified cancellation task contains circles or triangles interspersed evenly among similar shapes with small segments missing from the right or left side. Examiners instruct patients to simply circle complete shapes and cross out incomplete shapes. Patients who correctly circle or cancel shapes primarily on the array’s right side show performance consistent with viewer-centered neglect. In contrast, patients with stimulus-centered bias mark targets from both halves of the array but incorrectly circle incomplete shapes with segments missing from their left side (Figure 2). A recent examination of a large sample of HSN patients suggests that the majority of patients manifest viewer-centered symptoms.⁴⁰

In the clinical setting, examiners rarely identify patients with isolated stimulus-centered neglect. However, speech pathologists or occupational therapists may identify such patients while addressing reading or vocational problems. Until relatively recently, the independence of HSN in viewer- versus stimulus-centered coordinates remained unclear. Indeed, large patient series have confirmed the frequent coexistence of spatial bias respecting both reference frames. Research clearly documents double dissociations, however, with some patients’ whose behavior respects a stimulus-centered but not viewer-centered reference and vice versa.³⁹

The neurobiological autonomy of viewer- versus stimulus-centered spatial cognition may reflect a general organizing principle of visual processing. A widely accepted model proposes that dorsal (parietal) systems manage information relevant to stimulus location in preparation for action (the “where” system), while ventral (temporal) stream functions contribute more to stimulus identification (the “what” system).⁴¹ Convergent evidence shows that dorsal and ventral systems respectively encode space based on viewer-centered and stimulus-centered reference frames. Single unit recordings in monkeys, for example, reveal parietal neurons that selectively respond to spatial position with reference to the body.⁴² Research in normal humans

also supports anatomical distinctions between viewer- and stimulus-centered processing. Using transcranial magnetic stimulation (TMS) to transiently disrupt neural activity, Muggleton and colleagues impaired viewer-centered target detection through stimulation of right (but not left) posterior parietal cortex.⁴³ Conversely, TMS of right superior temporal cortex impeded performance on a “hard feature” search visual task that requires serial inspection of individual objects.⁴⁴ Congruent results were also recently reported during intraoperative inactivation of the superior temporal gyrus.⁴⁵ Functional magnetic resonance imaging (fMRI) studies also sustain the relationship between dorsal-ventral visual streams and attentional reference frame. For example, Fink and associates observed differential fMRI activation when healthy subjects made judgments of center for one- and two-dimensional stimuli.⁴⁶ Line center judgments activated right parietal cortex while square center judgments activated lingual gyrus, indicating ventral involvement as a stimulus becomes more “object-like”. A more recent fMRI experiment revealed parietal activation in a virtual-reality simulated environment during tasks requiring viewer-centered judgments, while stimulus-centered attention invoked neural activity in ventral occipitotemporal regions.⁴⁷

The effect of sensory-attentional versus motor-perceptual processing

Two distinct behavioral-physiologic processes may contribute to the “class common” spatial neglect, produced in experimental animals from rats to primates.⁴⁸ The key components of successful spatial cognition and recovery from HSN may be described as 1) optimal capacity to respond to perceptual-attentional information from the environment (“where” function) and 2) a physiologic permissive state enabling appropriate initiation and execution of motor-intentional “aiming”. Evidence supporting this distinction comes from observing within-task dissociations induced through experimental decoupling of the two components.

Several investigations have demonstrated how some stroke survivors with HSN exhibit defects of “where” perceptual-attentional function, hypothesized to be highly feedback dependent. All studies share a common methodology of contrasting performance on clinical tests, such as line bisection, in standard (or congruent) conditions to spatial bias obtained when viewing stimuli via devices that right-left reverse the direction of hand movement (incongruent condition).^{49–52} Patients with perceptual-attentional (“where”) dysfunction show bias determined by the viewed stimulus’ orientation independent of movement direction. Thus, in incongruent conditions, such patients make leftward bisection errors or omit right-sided cancellation targets, as these aspects of the page correspond to the right side of their view. In other individuals, the direction of hand movement determined spatial errors irrespective of what was perceived; performance is similar between congruent and incongruent conditions. Findings in this group indicate that their spatial neglect may signify defective motor-intentional “aiming”.

Compelling support for a distinct motor-intentional “aiming” component of HSN comes from animal research into the relationship of dopamine transmission and spatial attention. Animal experiments consistently show that unilateral lesions of ascending dopaminergic pathways induce behavior resembling the motor-intentional defect in some patients with spatial neglect.^{53,54} Relatively less is known about the specific neurobiological substrates of systems that mediate sensory-attentional “where” processes. Lesion studies in patients provide some indication that posterior parietal and temporal injuries correspond to neglect consistent with perceptual-attentional dysfunction. In contrast, patients with predominant deficits of the motor-intentional “aiming” component tend to harbor prerolandic and striatal damage.^{51,52,55} Other studies failed to identify separable lesion sites correlating with motor-intentional versus perceptual-attentional distinctions.⁵⁶ Hence, a discrete neuroanatomical foundation of “where” versus “aiming” processing remains unestablished.

The effect of distance

Another source of subject heterogeneity in neglect relates to the distance from the body of spatial computations being assessed. Current models of spatial cognition segregate space into three relatively discrete zones.²⁴ Personal space refers to the body surface area. Extrapersonal environment can be dichotomized into space within reaching distance (e.g., near extrapersonal or peripersonal) and space beyond reach (e.g., far extrapersonal). Single unit recordings in monkeys support the neurophysiological validity of these distinctions, documenting separate cortical areas that contain populations of neurons responding as a function of distance from the animal.⁵⁷ Experimentally induced lesions in monkeys also provide evidence for the neurobiological partitioning of peripersonal from extrapersonal space.²⁴ Specifically, resection of the frontal eye field impedes responses to contralesional stimuli in extrapersonal space, while similar lesions in adjacent prefrontal cortex compromise attention restricted to peripersonal space.

In human patients with brain injury, HSN may influence behavior across different ranges of proximity. Patients may lack awareness of their contralateral body, referred to as “personal” neglect, failing to comb hair on the left side of their head and shave or apply makeup only on the right side of their face. While peripersonal neglect may be identified with routine clinical tests, detection of HSN for far extrapersonal space is usually accomplished through effector extension. One convenient method entails, for example, having patients aim a laser pointer at the midpoint of lines located well beyond reaching distance, modified to subtend the same visual angle as lines in peripersonal space.^{58,59} Note that effector extension can alternatively be achieved by having individuals interact with stimuli in extrapersonal space through pointing with a rod. Using a laser pointer versus a rod may fundamentally alter the task, however. Studies demonstrate that the rod, acting as a tool, may “remap” far space into near space.^{60,61} Patients may, for example, show neglect in far extrapersonal space when bisecting lines with the laser pointer but perform without bias when contacting the line with a rod. Contrasting the two techniques, one recent study reported that the laser pointer, lacking sensory continuity between effector and target, may cause the opposite remapping of near space into far space.⁶² Other methods can minimize visuomotor demands through asking subjects to verbally report the identity or position of targets.^{63,64} In a similar fashion, the advent of virtual reality technology simulating peripersonal and extrapersonal space may afford a novel means for investigating the effect of proximity on spatial cognition without the encumbrance of laser pointer or rod.^{65,66}

Results of several studies of large samples of right hemisphere stroke patients show that peripersonal neglect is the most commonly encountered variety, either in isolation or combined with personal neglect.^{1,7,28} Research, primarily on single cases, demonstrates within-task double dissociations between spatial bias as a function of proximity. Examples include patients with severe neglect of personal space who perform normally on clinical tests of HSN.⁶⁷ Other reports document patients with right hemisphere injury who show bias when tested in peripersonal space but not extrapersonal space and vice versa.^{58,68} Limited lesion analysis data suggests an anatomical distinction between such patients, associating extrapersonal neglect with parietal injury and peripersonal neglect with more ventral damage involving frontal and temporal structures.⁶³

Investigations in normal subjects, using functional imaging and induction of “functional lesions” with TMS, confirm similar distinctions between neural coding of near and far space. Using positron emission tomography (PET), Weiss and associates demonstrated increased activity in dorsal occipital and intraparietal cortex when healthy subjects bisect lines and point to stimuli in near space.⁶⁹ The same tasks performed in extrapersonal space, by contrast, evoked activation of ventral occipital and medial temporal regions. Repetitive TMS over analogous

right hemisphere sites caused significant rightward shifts in normal subjects' perception of midpoint on prebisected lines.⁷⁰ In agreement with PET findings, stimulating posterior parietal cortex biased judgments only in near space while ventral occipital stimulation compromised task performance only for lines presented in extrapersonal space.

To recapitulate, subject heterogeneity in HSN depends on a multiplicity of factors, any combination of which may be operative in the individual patient. Important determinants of spatial behavior comprise task-related variables, such as the specific tests administered, and patient-related variables including reference frame and proximity in space. The next section briefly introduces some of the fundamental cognitive processes hypothesized to govern normal allocation of spatial attention and how their malfunction may contribute to HSN across the spectrum of heterogeneity reviewed above.

Psychological operations relevant to directed spatial attention - orienting

Complex nervous systems have evolved mechanisms for rapidly detecting unfamiliar or novel stimuli while inhibiting automatic responses to stimuli without behavioral significance.⁷¹ While far from perfect, paper-and-pencil tests of spatial neglect, such as target cancellation, exercise some of these functions relevant to daily activity (e.g., searching for a specific item on a cluttered desk). For the past two decades, researchers have more precisely parsed mechanisms relevant to deployment of attention across space through analysis of response to cueing. A comprehensive review of the vast literature pertaining to orienting biases in HSN far exceeds the scope of this review. However, some familiarity with spatial cuing paradigms may facilitate an understanding of contemporary research in HSN. Although more technology-intensive than standard clinical tasks, their brief duration and modest motor demands render them far more suitable for integration into evoked-response designs necessary for fMRI or electrophysiological investigations.

Stimuli that anticipate subsequently presented targets (i.e., cues) modulate response speed and accuracy, either advantageously or adversely.⁷² Cues that predict target locations ("valid" cues) decrease reaction time (RT), whereas cues that initially distract attention away from the target's eventual location ("invalid" cues) impede responses. Researchers can experimentally evaluate distinct attentional operations through manipulating the cue validity ratio.⁷³ For example, predictive cues (valid:invalid ratio $\geq 70\%$) evoke voluntary or "endogenous" orienting, resulting in response facilitation (valid RT < invalid RT). In contrast, cues lacking predictive value (valid:invalid ratio = 50%) facilitate responses due to reflexive or "exogenous" orienting. In addition to manipulating cue validity, task modifications can elicit either covert attention (cues appear at fixation) or overt attention (cues appear in the periphery).

A substantial amount of information about HSN has been generated through comparison spatial cuing function in patients and normal subjects. Posner and others discovered, for example, that patients with parietal lesions respond particularly slowly, or "reorient", to contralesional targets preceded by invalid cues, a finding termed the "disengage deficit".⁷⁴ While disengage deficits can be observed after parietal injury regardless of the presence or absence of neglect, the degree of response slowing to invalid cues has been correlated with neglect severity on clinical tasks in some but not all investigations.^{75,76} Subsequent research further established that problems neglect patients exhibit in disengaging attention from ipsilesional stimuli pertain especially when stimulus parameters elicit reflexive or exogenous orienting to peripheral cues.^{77,78}

Some investigators assign particular primacy to the disengage deficit, hypothesizing that it may provide a unifying account of spatial neglect. However, other observations make such positions untenable. Most critically, disengagement problems may help explain spatial bias once attention is already engaged ipsilesionally, but fail to address what "captures" attention in the first place. Sieroff and colleagues recently published data for other orienting processes relevant

to this issue.⁷⁶ Specifically, spatial cuing experiments reveal that neglect patients also manifest an “engagement deficit”, whereby responses following valid cues from or toward contralesional space are slower than ipsilesional valid cues. Defective engagement of attention toward contralesional stimuli may at least partly contribute to the “pathological attraction” to ipsilesional space characteristic of HSN.⁹

Cuing paradigms illustrate how the brain rapidly detects novelty and rejects of extraneous information. While such millisecond operations support the efficient allocation of attention across space, other data demonstrate that non-lateralized functions operating over a much larger time frame may also contribute to neglect behavior.⁷⁹

Psychological operations relevant to non-lateralized attention – alerting

Clinicians and therapists readily recognize how problems with alerting and sustained attention impede interactions with neglect patients. Alerting involves sustained changes in an organism’s internal state that prepare for stimulus reception and encompasses several forms.⁸⁰ A state of general wakefulness (tonic arousal), related to circadian mechanisms, can be transiently modulated through external stimuli (phasic arousal). Some authors also include sustained attention and vigilance as self-initiated, cognitively controlled aspects that promote and maintain arousal level.⁸¹ Alertness and sustained attention, considered spatially “non-lateralized” neural functions, are considered an obligatory prerequisite to the more complex lateralized processes mediating attention distribution across space.

Several lines of evidence sustain the position that impairments of nonlateralized attention contribute to HSN. Robertson and associates have conducted a number of studies that document deficits of alerting and sustained attention unconfined to specific spatial locations. For example, performing a monotonous tone-counting task, patients with right hemispheric stroke perform significantly worse than those with left hemisphere damage.⁸² In another experiment, patients with right brain injury made judgments between centrally presented sounds differing in time. Compared with controls, patients showed impaired tone discrimination, even with stimuli separated by gaps of 1500 ms.⁸³ Moreover, discrimination deficits were identified only in patients with neglect in this particular study.

A number of investigations confirm a strong statistical relationship between defective arousal or sustained attention and neglect severity.⁸⁴ Sustained attention also improves as patients with neglect recover but remains impaired in those who do not.⁸⁵ Some contradictory findings exist, however, showing that sustained attention may be demonstrated in patients with right hemisphere injury without HSN.⁸⁶ Although these discrepant observations imply that abnormal alerting may be necessary but not sufficient for the clinical expression of neglect, another recent investigation reported findings that may partly explain inconsistency between prior studies.⁸⁷ In healthy subjects, reduced arousal caused by sleep deprivation significantly slowed reorientation to left visual hemispace. Importantly, bias was only observed in far but not near space. Because previous studies assessed task performance in peripersonal space, negative findings may relate to such technical detail.

Additional nonlateralized processes relevant to neglect - time and memory

While most research on HSN focuses on problems deploying attention across space, several studies over the past decade also illustrate limits on deploying attention across time.⁸⁸ Evidence comes from the “attentional blink”, a refractory period that must elapse between two sequentially and rapidly presented targets for their detection. Normal individuals detect a second target only after ~400 ms, presumably due to a transient misallocation of attention to the later target while completing attentive processing of the first target. In contrast, patients with neglect show that substantially longer time must elapse between targets for accurate

identification.⁸⁹ While many authors attribute such findings to deficits of sustained attention, a more recent single-case study qualifies this conclusion. Specifically, Hillstrom and others found that a patient with HSN exhibited prolonged attentional blink only when the second target appeared contralesionally, while the refractory period was actually shorter than control subjects when presenting the second target ipsilesionally.⁹⁰ Other results consistent with problems allocating attention across time include performance in temporal order judgment. This paradigm requires subjects to determine which of two stimuli presented, with variable delay, to left and right of central fixation appear first. Subjective simultaneity, indicated by the delay at which individuals make equal right and left responses, corresponds closely to objective simultaneity in normal healthy subjects. Patients with neglect, on the other hand, judge stimuli as synchronous only when left targets precede the right by over 200 ms.^{91,92}

Studies indicating that HSN compromises deployment of attention over time indicate that patients may suffer fail to sustain mental representations, raising the related issue of spatial working memory. A modified cancellation task, wherein patients with HSN erased rather than marked each detected target, provided initial support for faulty spatial working memory.⁹³ When compared to standard cancellation, eliminating targets resulted in fewer contralesional omissions. A more recent experiment contrasted traditional cancellation performance to a task using “invisible” marks that left no trace on the array, but marked the underside via carbon paper underneath the page.⁹⁴ Patients with neglect contacted far fewer targets in the invisible cancellation condition. These findings could represent release of patients’ attention from “engagement” by ipsilesional targets. Alternatively, the data may imply that spatial memory deficits aggravate spatial bias, abetting recollection (through elimination) of erased targets or compromising the ability to recall that invisibly marked sites had already been searched. More recent investigations that eliminated confounds inherent in the modified cancellation tasks (i.e., spatial laterality, distractors) affirmed the relevance of spatial working memory. Ferber and Danckert, for example, asked patients with HSN to remember the location of vertically aligned shapes or numbers presented to the right hemifield.⁹⁵ After even brief delays, patients were significantly less accurate than controls in recalling spatial location but performed comparably with respect to number identity.

Other recent examinations of spatial working memory in spatial neglect were inspired by an unusual feature of cancellation on the ipsilesional, or “good”, side of the array. Specifically, neglect patients frequently mark ipsilesional targets multiple times as they redundantly search the same space.⁹⁶ One explanation of this singular behavior, rarely observed in healthy subjects, proposes that HSN relates to defective memory of prior search space. Research using eye-tracking techniques revealed that a patient with neglect pathologically “revisited” targets in the ipsilesional field, even when instructed to avoid gazing at previously viewed targets.⁹⁷ More recently, Mannan and colleagues examined whether recursive search of ipsilesional targets reflects spatial memory dysfunction rather than other potential mechanisms (e.g., executive dysfunction with perseveration).⁹⁸ When patients with neglect were required to press a response key only when they fixated a target in an array the first time, over half mistakenly identified previously located sites as new discoveries. Analysis of revisiting over time revealed a distinction between patients with anterior versus posterior lesions. Specifically, those with inferior frontal injury exhibited repetitive responses that were stable or decreased over time. In contrast, individuals with parietal damage displayed an increased probability of repetition as a function of time elapsed, suggesting that defective spatial memory may be particularly relevant to neglect after posterior cortical injury.

To summarize, contemporary neglect researchers can now seek unifying themes and consider more cohesive frameworks to model brain-behavior relationships. Investigators previously focused on extrapolating such principles from single, unique aspect of HSN, resulting in fractionation of theoretical positions. In contrast, current investigators consider neglect as

consisting of an admixture of component of lateralized and non-lateralized deficits, with the specific combination varying from patient to patient. Furthermore, the constituent defects presumably bear some tangible correlation to the location and extent of brain injury as reviewed below.

Correlating structure with behavioral dysfunction in neglect

As mentioned in the introduction, the association of HSN with right hemisphere injury remains the least controversial anatomical correlate, at least in the postacute period.⁹⁹ Patients may exhibit right-sided neglect after left brain lesions, though with lower incidence, severity and persistence.⁹ Tenets of neurological localization attribute HSN to damage within posterior aspects of the right cerebral cortex, including temporoparietal junction and inferior parietal lobule.^{2,100,101} However, injury to multiple discrete cortical and subcortical structures has also been associated with neglect behavior.^{102,103} Models of spatial attention reconcile the disparate locations of lesions associated with HSN through incorporation into large-scale, distributed networks whose components contribute to different aspects of spatial attention.¹⁰⁴ Recent studies challenged conventional principles, emphasizing a brain region not prominently featured in prevailing theoretical frameworks. Specifically, Karnath and colleagues reported an association of HSN with injury centered on the right superior temporal gyrus more rostral than those customarily linked to the disorder.¹⁰⁵ These results were subsequently criticized on the grounds of patient selection and image analysis methods.¹⁰¹ However, Karnath's group replicated their original findings in a larger group of subjects with acute right hemisphere stroke. Using voxel-based analysis, patients with neglect showed injury in superior temporal cortex, as well as the adjacent posterior insula and caudate/putamen.¹⁰⁶

As described in earlier parts of the review, subject heterogeneity in HSN makes detailed deficit characterization of potential significance for clinical-anatomic correlations. Several recent investigations that explicitly defined neglect reference frame (viewer- versus stimulus-centered) and part of affected space (personal versus extrapersonal) may help reconcile the views of authors who attribute HSN to parieto-frontal lesions and the recent evidence implicating some relationship to temporal lobe damage.

In one set of studies, Hillis and colleagues employed perfusion- and diffusion-weighted MRI methods to assess HSN within 48 hours after stroke. This approach, measuring both tissue infarction as well as adjacent areas of reduced blood flow, has furnished evidence that that cerebral dysfunction associated with spatial neglect reflects the conjoint consequence of low perfusion and ischemic damage. For example, the volume of hypoperfused tissue correlates strongly with performance on a battery of clinical measures of HSN.¹⁰⁷ Similarly, increased perfusion during recovery correlates significantly with improved target detection on cancellation tasks.¹⁰⁸ Most importantly from the perspective of neglect heterogeneity, lesion correlations with neglect characteristics revealed anatomic distinctions based on the reference frame that spatial bias respected. Whereas patients with viewer-centered neglect showed infarction and/or hypoperfusion in right parietal structures (angular and supramarginal gyri), stimulus-centered neglect was associated with abnormalities in superior temporal cortex.⁷

Mosre recently, Committeri and others reported lesion anatomy in neglect using a novel, voxel-based analysis (lesion-symptom mapping).¹⁰⁹ Their methodology allowed statistical covariation of neglect in personal from extrapersonal space (and vice versa), and established dissociations between the two types. Personal neglect was associated with lesions involving the postcentral and supramarginal gyri as well as subjacent white matter tracts. In contrast, patients with extrapersonal neglect demonstrated more rostral perisylvian damage, including the superior and middle temporal gyri, white matter deep to temporal cortex, the dorsolateral prefrontal cortex and inferior precentral cortex. Besides verifying the importance of detailed

characterization of neglect behaviors, their findings imply a key role of injury to subcortical fiber paths.

Previous clinical-radiographic correlations in HSN also emphasized disrupted connections between nodes of a hypothetical spatial attention network.^{101,110} Evidence derives partly from neglect after posterior cerebral artery stroke. One study found, for example, that occipital injuries causing left hemianopia and spatial neglect involve structures beyond striate and extrastriate cortex (thalamus and posterior corpus callosum).¹¹¹ In a more recent analysis, an area of damage within the deep occipital white matter, possibly corresponding to the inferior occipital fasciculus, was identified in all patients with neglect but spared in every control.¹¹² Another fiber pathway relevant to HSN was also preliminarily identified through diffusion tensor imaging.¹¹³ Data from this small sample suggests that lesions in the inferior fronto-occipital fasciculus may contribute to neglect. A recent meta-analysis of previous lesion mapping studies ascertained that white matter in the superior longitudinal fasciculus may be a critical nexus of brain injury associated with HSN.¹¹⁴ While coherent themes remain difficult to discern, white matter projections implicated in neglect reciprocally interconnect inferior parietal and temporoparietal regions with dorsal (superior parietal, dorsolateral prefrontal) or ventral (superior temporal, ventral prefrontal) cortical nodes relevant to spatial attention. Further, a point not stressed to date is that interruption of subcortical fiber tracts likely also interrupts ascending mesencephalic-thalamic projections important for arousal and alerting.

Disconnection within a distributed spatial attention network may account for a discrepancy between human lesion studies and functional imaging of normal spatial cognition. Specifically, normal subjects performing spatial attention tasks activate cortical regions that, depending on cue validity, correspond inexactly with lesion loci in patients with HSN. Valid cues engage the frontal eye fields and the posterior-ventral intraparietal sulcus, regions more dorsal than those associated with spatial neglect.¹¹⁵ Areas responsive to invalid cues, by contrast, recruit ventral locations (precentral sulcus, middle frontal gyrus, temporoparietal junction, superior temporal sulcus) relevant to lesion sites implicated in HSN. Conspicuously missing are event-related activations in a number of regions identified in lesion mapping studies of patients with spatial neglect (e.g., supramarginal and angular gyri).

Recent findings from Corbetta and associates may account for how damaging one component of the spatial attention network may disturb function in anatomically remote sites. One fMRI study examined brain activity evoked by spatial orienting in patients with HSN during acute and recovery periods.¹¹⁶ Shortly after injury, patients showed reduced activation of ipsilesional, uninjured dorsal parietal cortex and hyperactivity in homologous contralesional areas. Authors hypothesized that interhemispheric imbalance between dorsal networks underlies spatial bias in neglect. Recovery was correlated with “normalization” of evoked signals and more balanced of activity. More recently, the same group evaluated functional connectivity measures in acute and post-acute stages in patients with spatial neglect.¹¹⁷ Shortly after injury, disrupted connectivity was demonstrated between left and right dorsal parietal regions identified in their earlier study. Significant inverse correlations were observed between dorsal connectivity measures and detection of contralesional targets following invalid cues. Abnormal connectivity between ventral components (i.e., left and right supramarginal gyrus) was also documented and correlated significantly with connectivity between the more dorsal sites. Intrahemispheric connectivity measures between middle frontal and superior temporal cortex exhibited a similar statistical relationship to interhemispheric connectivity between parietal regions. In the post-acute stage, connectivity measures between intraparietal regions returned to age-matched control values while disrupted functional connectivity in the ventral components did not recover. Authors concluded that findings support their contention that successful spatial orienting requires interhemispheric coordination between dorsal and ventral components of the attentional network

While advances in neuroimaging technology continue to provide new insights into neglect neurobiology, caveats regarding conclusions should be kept in mind. Differences in patient selection, time between injury and imaging, and methods of localizing specific structures or identifying regions of interest vary across every study cited above. Such confounds render comparisons between research groups tenuous and potentially undermine integration of multiple observations into cohesive interpretations and models.

Rehabilitation of neglect – a work in progress

Enduring neglect poses considerable obstacles to successful rehabilitation outcomes.^{118,119} A number of studies document that when patients have HSN, they demonstrate greater impairment on disability measures, their caregivers experience greater burden, and patients require more prolonged rehabilitation compared to those without neglect.^{120,121} Because of the large number of patients affected by neglect, effective rehabilitation that reduces care costs would result in substantial monetary savings.

Natural history studies show that spontaneous improvement in neglect behaviors plateaus about two months after injury.¹²² However, another more recent report observed continuous recovery in a subset of neglect patients up to six months after injury.¹²³ Furthermore, evidence exists that differences in treatment response do not appear to depend on time since injury or the brain lesion's size or anatomic distribution.¹²² Hence, rehabilitation efforts may be considered in individual patients even with large, severe injuries and even months or years after onset.

Unfortunately, no consensus exists regarding evidence-based recommendations for spatial neglect rehabilitation. No interventions have yet been subjected to large-scale, multi-site, randomized controlled clinical trials.⁷ Accordingly, the most Cochrane review of neglect rehabilitation concluded that currently available studies lack sufficient data to either support or refute efficacy to reduce disability or enhance independence.¹²⁴ Two major challenges complicate such trials' design. First, the broad constellation of neglect symptoms may undermine the power of outcome analyses based on group-averaged data. Second, because neglect may improve spontaneously, the item-level validity and reliability of nearly all neglect assessment measures must be more comprehensively established. Other study designs may, in fact, be more suitable for evaluating neglect treatments. For example, "N of 1" designs explicitly consider individual variability in a manner that subjects acts as their own control. Unfortunately, evidence-based reviews exclude such designs from meta-analysis and deem similar quasi-experimental strategies inferior. The medical and research communities may thus need to relinquish their preference for randomized, controlled methods appropriate for drugs and devices when studying treatments for HSN.

Several additional reasons may explain why neglect rehabilitation studies have thus far met with qualified success. The first issue regards generalization of training to situations outside the laboratory. Although consensus exists that treatment (of several types, reviewed below) may improve spatial neglect symptoms, limited information is available about beneficial effects on daily function.¹²⁵ A number of interventions result in more accurate performance on tasks similar to those used in training but fail to improve behavior in more attentionally demanding real-world situations.³ With regard to tailoring interventions to specific patients, subject heterogeneity described in preceding sections, has been underemphasized in most studies to date. If dissociable systems mediate different neglect manifestations, then subject heterogeneity, the primary mechanisms addressed by a specific therapy and the tasks selected to measure response must all be considered. Unfortunately, characterizing spatial neglect in detail necessitates a considerable investment in time and effort. For example, a recent study recommended administering a minimum of ten different tests to detect HSN, characterize performance dissociations, and grade severity.²⁸ Furthermore, therapy programs comparable

to those reported in the literature may not be feasible in most rehabilitation hospitals clinics in terms of duration of treatment sessions and frequency of administration.

Treatments of neglect can be classified broadly into approaches either directed at “top-down”, goal-driven mechanisms and those based on “bottom-up”, stimulus-based techniques. In general, top-down therapies require patient agency and taking an active role in implementing newly learned cognitive strategies to compensate for spatial bias.¹²⁶ An obvious prerequisite for such training, however, is that patients retain some awareness of deficits. The frequent association of HSN and anosognosia may thus limit the utility of top-down therapies for many individuals (though see reference 127 for contrary evidence). Bottom-up or stimulus-driven methods, by contrast, are more passive in nature and require less active patient participation. Such strategies aim to reconfigure or enhance external stimuli, potentially through rectification of biased representations.¹²⁸ Note that theoretical considerations and limited empirical data suggest that combining both top-down and bottom-up interventions may act synergistically compared with either class of therapy administered in isolation.^{88,129}

The most widely employed spatial neglect treatment emphasizes top-down mechanisms, mainly based on visual scanning training. Therapists encourage and remind patients to orient leftward during various visuospatial tasks, often supplementing verbal instructions with tactile, auditory or visual prompts (see reference 122 for more detailed description). Scanning therapy can take several different forms. At one extreme, training consists primarily of insight-oriented verbal instruction; at the other, instructions may be incidental to eye movements and motor habit learning. One evidence-based review found that visual scanning training was the approach most often linked to improved performance on target cancellation and line bisection tests.¹²⁴ While no specific procedure can be recommended, a recent review provided several conclusions about visual scanning therapy.¹²² First, successful intervention requires protracted training (e.g., 40 sessions over 8 weeks) to achieve high levels of over-learning. Indeed, the majority of trials reporting negative results employed brief treatment durations.¹³⁰ Second, programs that stimulate contralesional space exploration produce greater improvements than the restricted use of verbal prompts or instruction. Lastly, training programs may induce domain-specific benefits related to the neglect reference frame. Therapeutic benefits of scanning therapy, for example, appear confined to exploration of extrapersonal space without benefit for personal neglect.¹²⁷

Some rehabilitation strategies target both top-down and bottom up mechanisms through modifying nonlateralized deficits of alerting. One study invoked phasic alerting through presenting unpredictable, centrally presented warning tone bursts to eight patients with HSN after right hemisphere injury.¹³¹ Sounds preceded 25% of trials by 300–1000 ms while patients performed a visual temporal order judgment task. Warning tones normalized the threshold for subjective simultaneity in all patients, even leading to an advantage for left over right events in a subset. Remarkably, the same results obtained even when the speaker was positioned far to the right. Thim and others recently published the results of alertness training in seven patients with evidence of neglect and reduced vigilance.¹³² Patients underwent training with the “AIXTENT” program, essentially a driving simulation requiring patients to avoid obstacles that suddenly appeared to their left and right. Most patients improved performance on clinical neglect assessments, though benefits failed to persist four weeks after training ended. An alternative approach described how therapists intermittently prompted eight neglect patients as they performed tasks requiring sustained attention (e.g., sorting cards). With time, therapists shifted the responsibility for prompting to the patients. Therapy resulted in gains in measures of both sustained attention and neglect, though the duration of treatment effect was not established.

Bottom-up treatment strategies capitalize on the fact that several different types of sensory or sensorimotor stimuli reduce neglect behavior.¹³³ Techniques include cold caloric stimulation of the contralesional ear, vibratory or transcutaneous electrical stimulation to left paracervical muscles, and optokinetic stimulation with leftward moving backgrounds.^{134–139} Importantly, some of these procedures can aggravate spatial bias if not properly administered (e.g., cold caloric stimulation of the ipsilesional ear). Vestibular-proprioceptive stimulation methods share a number of features. First, besides amelioration of neglect, stimulation reduces both basic sensory impairments (e.g., hemianesthesia) as well as more complex associated phenomena (anosognosia, somatoparaphrenia). Second, peripheral stimulation may influence viewer-centered HSN without modifying stimulus-centered bias. Third, the effects of stimulation persist over a variable, but typically brief, period. The relatively short-lived effects lead some authors to consider such techniques as not relevant for rehabilitation.¹⁴⁰ However, durable effects have been documented for some of these techniques. Furthermore, even temporary remission of anosognosia might facilitate participation in, for example, visual scanning therapy.

Pharmacotherapy might also be considered a form of bottom up intervention. Converging evidence implicates catecholaminergic deficiency as relevant to both spatial and nonspatial attention disorders in HSN (see reference 128 for review). Research regarding drug treatments has produced conflicting results, however. Three studies demonstrated that dopamine (DA) agonists temporarily ameliorate neglect behaviors.^{141–143} In contrast, other investigators reported that similar agents in varying doses actually exacerbate HSN, perhaps via overactivation of uninjured DA systems in the ipsilesional hemisphere.^{144, 145} Relatively less is known about the potential of medications that modulate norepinephrine (NE) transmission. One study found that methylphenidate, a compound that alters both DA and NE levels, improved HSN but not to the same extent as the DA agonist bromocriptine.¹⁴¹ Most recently, Malhotra and others administered guanfacine, a NE agonist, to three patients with HSN in a double-blind trial and observed that two patients detected contralesional targets significantly better after guanfacine than placebo.¹⁴⁶

Methodological issues, unique to pharmacotherapy, may help reconcile discrepant findings from previous studies. Because NE binds with highest affinity to α_2 receptors, low levels released during normal alertness stimulate α_2 receptors.¹⁴⁷ Higher frequency discharge results in greater NE binding at low affinity α_1 and β receptors, opposing the effect of α_2 stimulation. While α_2 binding is posited to improve “signal-to-noise” ratio in prefrontal cortex, stimulation of α_1/β receptors impairs function in the same regions, potentially in service of reflexive behaviors conducive to “fight-or-flight” circumstances. Hence, NE exhibits an inverted-U-shaped concentration-response curve; either deficiency or excess adversely affects normal attention. Note that similar considerations pertain to DA and acetylcholine. Accordingly, future studies will benefit from identifying “optimum” dose ranges for a given agent. Pharmacodynamic properties may also determine response. For example, Parton and colleagues point out that DA agonists evaluated to date stimulate either D2 receptors (bromocriptine) or both D1 and D2 sites (apomorphine).³ Because animal studies indicate that D1 receptor activity is most important for modulating spatial working memory, future drug trials might improve efficacy through administration of more selective agonists. Similarly, guanfacine may be a particularly suitable NE agonist because of its relatively high potency at α_2 receptors.

Prism adaptation provides a promising bottom-up approach to neglect rehabilitation. When individuals donning prismatic lenses displacing their vision 10–12 degrees horizontally point to a viewed target, they initially misdirect their hand in the direction of optical shift. Repeated attempts to point (provided that the hand and arm are obscured from view except for the final few degrees of movement) produce rapid reduction of error through visuomotor adaptation, a

form of implicit motor learning. After removing lenses, pointing error temporarily reverses direction, a phenomenon termed the “aftereffect”. Adaptation is strongly correlated with a therapeutic effect of prism adaptation on spatial neglect^{148–150}, and is dependent upon low-level, ballistic visual movement planning, as conscious, strategic attempts to alter movement direction reduce adaptation. Although the effects of prism adaptation are reported in individual patients to persist for months, as many as 25% of patients, or more, do not respond, and the treatment may be highly task-specific.^{150–152} A preliminary report of a randomized controlled trial of prism adaptation therapy for post-stroke spatial neglect¹⁵³ reported no benefit over standard behavioral treatment. However, the problems of reduced internal validity of randomized controlled trial design in heterogeneous subject groups experiencing continuous recovery may critically limit the ability of these kind of studies to detect significant results.

Concluding comments

In many respects, spatial neglect represents an excellent example of the challenges realizing a translational cognitive science. Ideally, a continuum of research from basic discovery to clinical application would promote understanding of normal spatial cognition while limiting individual patient’s morbidity.

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Figure 1. Patient with neglect after right brain injury fails to mark contralesional “A” targets in array of letters (A) and omits contralesional aspects of rendered figure (B).

Mapping—Participant is asked to "Mark Florida, California, Texas, Oregon and Maine on this map of the USA." This participant, with left spatial neglect after a right-cortical stroke, has positioned all of the states on the right side of the map regardless of their true location, consistent with a possible bias of internal representation (imagery).

Figure 2.

Patient with neglect after right hemisphere stroke positions west coast states [California (CA) and Oregon (OR)] on the right half of a contour of the United States, consistent with a rightward bias in spatial representation.

Figure 3.

(A) Viewer-centered neglect: patient correctly circles complete figure and cancels incomplete figures on contralesional side of the array (similar to Fig. 1A). (B) Object-centered neglect: patient marks targets on both sides of the array but incorrectly identifies incomplete figures (lacking a left-sided segment) as complete.

Figure 4.

Cortical sites implicated in spatial attention, including their putative specialization and distance/reference frames suggested in human lesion studies. TPJ, temporoparietal junction; STG, superior temporal gyrus; MFG, middle frontal gyrus; IFG, inferior frontal gyrus.