

ACUTE VERSUS CHRONIC FUNCTIONAL ASPECTS OF UNILATERAL SPATIAL NEGLECT

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TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Primacy of unilateral neglect for disability
4. Functional manifestations of unilateral neglect
5. Neglect recovery and chronic aspects of neglect
6. The functionally valid assessment of neglect
7. Rehabilitation of neglect
 - 7.1. Vestibular stimulation
 - 7.2. Eye patching
 - 7.3. Pharmacologic intervention
 - 7.4. Prisms
8. Discussion
9. Acknowledgments
10. References

1. ABSTRACT

This article reviews the impact of unilateral spatial neglect on daily living ("functional") activities. Its disturbances on basic functional activities, such as feeding, grooming, and locomotion, are easily identifiable. Patients with neglect frequently lack insight into their disorder and do not initiate compensatory behaviors, which probably impedes recovery. Simple standard tests of neglect during visual exploration correlate with impaired recovery of functional skills acutely following brain injury. However, unilateral neglect resolves in most individuals, yet many patients remain chronically impaired during daily living activities. This suggests that some other disorder associated with neglect may contribute to the failure to regain functional independence. A candidate disorder is general (non-spatial) inattention. However, cognitive studies in stroke are biased toward assessing neglect and are usually insensitive to other disorders that may accompany stroke, such as general inattention and executive dysfunction. Therefore, the contribution of unilateral neglect toward functional status relative to diverse other cognitive disorders after stroke is unclear. Treatments for unilateral neglect have been largely unsuccessful or impractical, or they were not evaluated in controlled studies. Intensive practice of scanning appears to benefit, but this observation needs to be replicated in a controlled manner. A recently developed treatment that involves wearing prisms to shift the view ipsilaterally has been associated with transfer of training effects to untreated spatial activities and prolonged improvement of neglect. However, despite some promising lines of investigation in neglect rehabilitation, further research is required to understand where neglect stands in relation to other cognitive disturbances that follow stroke with respect to functional significance and recovery, to decide what disorders should be targeted for rehabilitation.

2. INTRODUCTION

Unilateral neglect (alternately termed spatial neglect, hemispatial neglect, amorphosynthesis, hemi-inattention) has been recognized in humans since the early 20th century (1). Definitions vary, but essentially the term refers to pathologic spatial asymmetry in performance or awareness. This lopsidedness entails a *deficiency* for action or awareness that in most instances is contralateral to the side of brain injury. However, the individual with neglect in addition may demonstrate *overactivity* in the opposite direction (i.e., ipsilateral to the side of brain injury) (2-5). Neglect is considered to have an attentional basis, since it may be overcome by cuing or increasing motivation (6-15).

Unilateral neglect is commonly recognized by physicians, psychologists, therapists, and family members in individuals with brain injury. Furthermore, unilateral inattention can interfere with routine daily living activities, such as locomotion and feeding. This article will review the impact of neglect on daily living activities ("functional activities") both acutely and chronically following brain injury. For this article, "functional" will refer broadly to any voluntary activity that is involved with self-care, locomotion, social interaction, or self-fulfillment (e.g., leisure pursuits). This is to be distinguished from activity on tasks that are considered to be experimental or diagnostic, but without clear benefit to the individual (e.g., line bisection), or from primarily involuntary behaviors (e.g., dreaming, reflexive withdrawal to pain).

Although investigational and clinical reports often regard neglect as if it were a well-described and homogeneous phenomenon, investigators repeatedly have stressed that "neglect" comprises a heterogeneous array of disturbances, as does "aphasia." Inconsistencies may occur

Table 1. Literature citations associating specific cognitive disorders with impaired functional recovery following stroke

Cognitive disorder	References
Unilateral neglect	26-42
Depression	36, 43-49
Aphasia	36, 37, 50-53
Anosognosia (impaired insight into one's own illness)	39, 54-56
General inattention	57, 58
Disorientation	59, 60
Limb apraxia	50, 61
Memory impairment	60, 62
Pathologic laughter and crying	61
Motor impersistence	62
Executive dysfunction	63

Numerals denote specific citations given in the References section.

in its severity (16-18) or even *direction* (i.e., to the left or right) *within* an individual patient (19-25), depending on the task or what specific stimuli are presented. (However, neglect on functional tasks is almost invariably contralateral to the acute, major cerebral lesion.) Thus, the disturbances that are collectively referred to as "unilateral neglect" are considerably diverse and may have different neurophysiologic bases. This frustrates developing standards for diagnosing and reporting neglect. However, the absence of standard definitions for neglect does not undermine the clinical importance it has for the performance and recovery of functional activities.

3. PRIMACY OF UNILATERAL NEGLECT FOR DISABILITY

As would be expected with any cognitive impairment, functional disturbances may accompany neglect. However, neglect is especially important, since it has been associated with impaired functional recovery following brain injury more often than any other cognitive disorder. Table 1 reflects the importance that clinical investigators have attached to neglect following stroke. Although neglect may occur with nearly any illness that involves structural brain injury, it has most often been evaluated following stroke. (Stroke is defined as an enduring neurologic disorder of abrupt onset that is presumed to be secondary to a pathologic alteration of regional blood flow, such as from hemorrhage or blood vessel blockage.) This bias toward evaluating neglect following stroke is most likely due to the high prevalence of stroke and its increasing incidence as the mean age of populations increases, particularly in industrialized nations. Table 1 cites the articles from the author's own literature survey up to the year 2002 that have associated specific cognitive disorders following stroke with impaired functional recovery.

However, a ballot-counting measure of these citations cannot be assumed to reflect the actual comparative frequency of these cognitive disorders following stroke or the strength of their associations with functional decline. It is not possible to draw conclusions

from these studies on the primacy of unilateral neglect for functional outcomes after stroke because of inconsistencies in (1) the range of cognitive functions assessed, (2) the specific cognitive tests used, and (3) the functional assessments used. Moreover, the surfeit of studies on neglect may reflect a clinical and investigational preoccupation with its bizarre aspects (e.g., drawing only half a flower, denial of limb ownership) or the ease of its assessment relative to other cognitive disorders. (For example, neglect is commonly assessed by measuring the difference from true midpoint when subjects are asked to bisect lines with a pen, or by counting the number of omitted figures on cancellation tests, where subjects must cross out all figures of a certain kind.) Few studies that found disorders other than neglect to be importantly related to outcome actually examined for neglect (56, 57, 60, 61). In addition, measures of functional ability are biased toward basic motoric activities, and they less reliably or easily assess social, leisure, or community-based activities (e.g., banking, driving, or other "instrumental" activities of daily living). Thus, Table 1 at best reflects the present clinical and investigational appreciation for the impact of neglect on a restricted set of functional activities.

4. FUNCTIONAL MANIFESTATIONS OF UNILATERAL NEGLECT

Clinicians who treat brain-injured individuals readily associate neglect with functional impairment. Indeed, a disorder that seriously affects either the "input" or "output" aspects of directional spatial cognition might be expected *a priori* to impair *any* functional activity. Consequently, the functional impact of neglect is almost without limit. Some of the more common or interesting aspects of functional neglect are described below.

In its most severe form, neglect may involve a strong gaze bias that is directed ipsilateral to a unilateral hemispheric lesion. This finding, which has been termed "Vulpian's sign" (64), is often associated with a marked disinclination to orient or explore contralaterally, either visually or manually. (For the remainder of this article, "ipsilateral" and "contralateral" will be used with respect to the location of the brain lesion that is presumed to be responsible for the clinical disorder under discussion.) Ipsilateral gaze bias nearly always appears when the brain injury is acute, and the brain lesion is generally large and cortical, spanning most of a lobe or overlapping lobes. The impairment frustrates the most basic functional activities in the clinician-patient relationship, so that the patient fails to turn the head or eyes toward a clinician or family member who stands in contralateral space. The patient also often fails to find the contralateral hand with the ipsilateral hand upon command, and more often gropes only the contralateral chest or shoulder before stopping. An accompanying neglect *syndrome* usually appears in this severe state, which includes (1) flattening of affect and vocal intonation (aprosodia), (2) unawareness (anosognosia) for the severe hemiparesis and hemianopia that are usually coexisting, and (3) an apparent indifference to neglect itself after it has been pointed out. The latter is very surprising: patients fail to be impressed by the



Figure 1. Pusher syndrome in a man with left neglect while he performs a line cancellation test. This man habitually maintained the abnormal posture despite developing painful contracture of the neck.

clinician's pointing out their failure to orient past the body midline; they behave as if the world simply has stopped at the midline. They also fail to search for boundaries in their environment for spatial reference. Thus, for example, corners of rooms or the edges of food trays or pages hold no importance (19). Their failure to find the contralateral hand generally does not concern them either. Furthermore, when the clinician holds the (almost invariably) paralyzed hand in front of the patient's face, the patient will often deny that the hand belongs to him or her (somatoparaphrenia) (65, 66). In such instances, finding that the paralyzed contralateral hand cohabits the bed with them sometimes offends or frightens such patients, who demand to have the "stranger" or the arm taken away (67). Finally, they may also falsely localize a perceived stimulus on the neglected side. For example, clinicians may observe that when neglect patients are touched on the contralateral knee, the patients may state that they were touched on the abdomen. Similarly, they may believe that the person who speaks to them from their contralateral side is actually on their ipsilateral side. This false interpretation of stimuli without self-initiated verification amounts to confabulation.

As patients with severe acute neglect regain mobility, they frequently tilt the body or head toward the contralateral side. This phenomenon was termed the "pusher syndrome" by Davies (68), and clinical reports of it have recently become frequent (69-77). The consequence of the pusher syndrome frequently is dangerous maintenance of the body posture in bed or in the wheelchair, such that the patient risks falling to the floor. Torticollis may also result (14), which despite the accompanying pain from the prolonged dystonic neck posture may not be spontaneously overcome by the patient (figure 1).

As mobility recovers, neglect patients may fail to protect their hemiparetic limbs during locomotion. For example, neglect patients commonly dangle their hemiplegic upper limb over the arm rest of the wheelchair,

against the wheel. [However, although neglect frequently accompanies prolonged contralateral limb flaccidity after stroke (78), reports are inconsistent regarding the association between limb pain in hemiplegia and neglect (79) (80).] Conceivably, inattention to the paralyzed limb could lead to crush injuries when patients try to wheel through doorways, although this has not been reported in the literature. Neglect patients also commonly fail to protect the paretic limb during transfers from bed to chair or during mat mobility. Even when limb paresis is mild (as demonstrated by limb movement to command), neglect patients frequently fail to use the limb to assist themselves when balancing or during other activities. This failure of spontaneous limb use on one side has been termed "motor neglect" (81). It is clinically similar to "learned nonuse" in chronic hemiparesis (82), in which patients move the limb better to command than they do spontaneously. However, learned nonuse is thought to develop from punishing interactions with the environment after the patient initially experiences difficulty with moving the limb, whereas motor neglect is considered to involve an unlearned endogenous inhibition of unilateral limb activation (83).

Not surprisingly, neglect can disrupt locomotion over greater distances. The patient may veer to one side while walking (84). Grossi *et al* (85) observed that an 8-year-old boy with traumatic brain injury had unilateral neglect while he walked: he inadvertently knocked down objects that were mainly to his left. Nonetheless, the boy was unimpaired during standard neglect assessments. Similarly, individuals with homonymous hemianopia following brain injury may fail to scan contralaterally, despite the absence of contralateral neglect during standard tests. This deficit may be associated with impaired obstacle avoidance, particularly when crossing streets or walking along corridors, and can be behaviorally modified without substantially improving the visual field defect itself (86). [An open question is whether a unilateral deficit during functional tasks is truly "neglect" when there is no corroboration from standard neglect tests. If the deficit can be improved through improving attention, then the disorder would appear to qualify as neglect. But see Mark and Kerkhoff (87) for debate on this point and related issues. Tant *et al.* (88) also contribute data pertinent to this concern.]

In addition, patients with neglect are prone to falls and wheelchair accidents (89-94). Omissions on cancellation tests may be associated with impaired driving in stroke patients after discharge (95). One stroke patient with unilateral neglect on multiple kinds of tests was noted by his wife to inadvertently veer their car toward the right (96). Other case reports have described repeated traffic accidents by drivers with unilateral posterior hemispheric lesions who failed to monitor the environment contralaterally (97, 98). In general, though, stroke patients with chronic unilateral neglect do not drive, in contrast to stroke patients without neglect (99, 100). It is not yet clear whether such patients decide not to drive or are prevented by others from driving, and whether neglect itself or a different disorder is fundamentally why neglect patients do not drive or why they have vehicular accidents.

Functional neglect



Figure 2. Left personal neglect reflected in grooming. The patient's wife was asked not to assist him with shaving on the day that this photograph was taken. The right side of the face is clean shaven, the left side untouched. This man habitually groomed only the right side of his face.

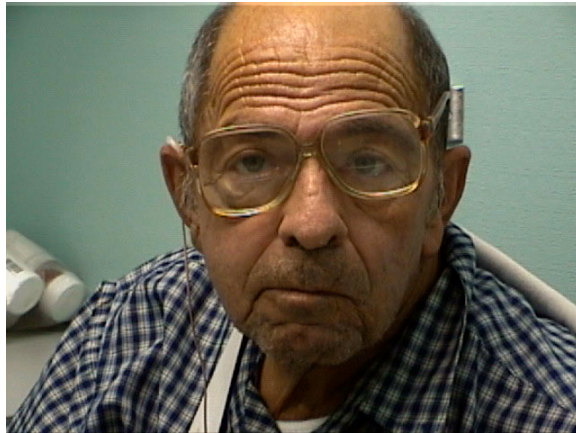


Figure 3. The "hanging spectacles" sign in the man shown in figure 3. His wife had observed that her husband was usually careless on his contralateral side when putting on his eyeglasses. He was asked to take off and then replace his eyeglasses without further instruction just before this photograph was taken.

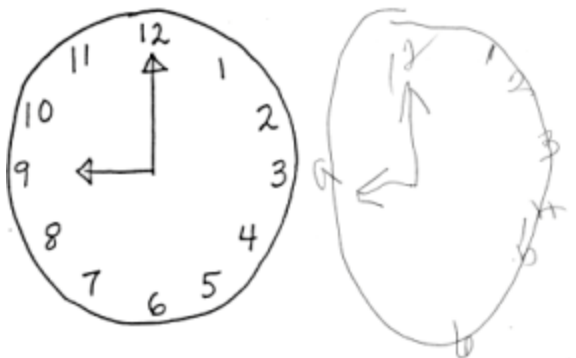


Figure 4. Unilateral neglect during clock drawing. The example is shown above and the patient's copy to the right. Not uncommonly, patients with left neglect sketch the entire circle and write the numerals 12, 3, 6, and 9 at their correct locations. The patient was satisfied that she had sketched the entire clock face shown to her. She acknowledged her omissions when they were indicated to her. Note the bunching of numerals on the right side, another characteristic of clock drawing by patients with neglect.

Neglect frequently appears during self-care activities. Pocketing food on one side of the mouth is commonly observed by rehabilitation therapists, despite its

having been reported only occasionally (101-103). Patients may also consistently overlook food items from one side of the plate. Disabled self-dressing ("dressing apraxia") is not unusual among patients with neglect (29, 104, 105), but whether the disorder usually results directly from hemi-inattention vs. a non-lateralized attentional or planning disturbance has not been ascertained. Self-grooming impairments are also common (figure 2). A peculiar finding is the "hanging spectacles" sign (106), in which the patient recurrently fails to place the contralateral frame of the eyeglasses behind the ear (figure 3). Similarly, a unilateral "hanging dentures" deficit has been described (107).

Because unilateral neglect is easily recorded and scored with graphomotor tasks such as line bisection and cancellation, it is not surprising that research reports of neglect during drawing or writing are legion. The classic graphomotor disturbances of neglect include biasing writing to one side of the page and supplying numerals primarily on one side of a clock face (figure 4). A popular test is to have the patient sketch a daisy, which typically results in omitting the petals on one side. Omissions in copying tasks can be either within individual objects wherever they occur in the scene or for entire objects that are on the contralateral side of the scene that is being copied (108) (figure 5). Examples abound of unilateral neglect in the works of professional graphic artists (109-111). Neglect within scenes may also appear when patients snap photographs (112). Chronically deaf patients with left neglect may show strongly asymmetric "mapping" when they describe their living quarters through manual signing (113). That is, they cluster their gestured productions to the right side of the space in front of them, which yields a markedly distorted representation of space akin to that found on drawing tasks. Remarkably, when they communicate non-spatial concepts through signing, deaf patients with neglect do not skew their use of space.

Not surprisingly, patients may also fail to read adequately due to neglect. Patients may read from only one side of the page. When they read aloud spatially isolated words, they may either omit the contralateral half of the word, or they may substitute an incorrect word that is identical to the target word only on the ipsilateral side. For example, when reading a compound noun such as "hot dog," they may say only "dog." "The" may become "he." In contrast, hemiconfabulated items can include "prize" instead of "satirize," "target" instead of "forget" (114). The consistent location of mistakes to one side of words is not explained by a purely visual disorder. Instead, the impairment reflects consistent carelessness with identifying word beginnings or endings. Many patients with neglect during reading (neglect dyslexia) fail to detect the thematic aberrancies that result when they read aloud.

Neglect may also disturb more complex activities, such as leisure pursuits. Neglect during chess playing has been described (115, 116). Unilateral inattention during card playing has been measured in the laboratory (102, 117) and thus may occur in the real world. Neglect also has been found on kitchen activities in the laboratory (27, 118-120).



Figure 5. Unilateral neglect when copying a scene, executed by the same patient from figure 5. Before she started copying, she was asked what she saw. She said, “A tree, a house, and a fence.” After she believed that she had copied the entire picture, she was asked again what she saw in the original picture: “A tree and a house.” Note not only the absence of figures from the left side of the scene, but also that only half the tree was drawn, thus demonstrating two different kinds of neglect on drawing tasks (i.e., environment-based neglect and object-based neglect). The distortion of elements in drawings (constructional apraxia), as shown here, is also common in patients with unilateral neglect.

5. NEGLECT RECOVERY AND CHRONIC ASPECTS OF NEGLECT

For the most part, the foregoing reports of neglect assessed patients acutely after illness onset, i.e., approximately within the first month. It is well known that neglect may persist, but the distinctions between acute and chronic neglect have not been comprehensively studied. During recovery, the neglected area on cancellation tests may shift either farther to the left or toward the near left quadrant of the page (121, 122). The error direction on line bisection tests may reverse with recovery (123-125), suggesting either overcompensation for neglect or the unmasking of other cognitive deficits as the original disorder recedes. However, reversals in neglect direction during other activities, including functional tasks, have not been reported during recovery.

One aspect of neglect that is more often encountered chronically than acutely is *awareness* for the disability (111, 126-128). This paradoxical state—nearly the opposite of anosognosia—amounts to “lip service” for the condition. That is, patients may readily admit, even volunteer details about their unilateral inattention, and yet fail to consistently and spontaneously compensate, such as by scanning bilaterally or attending to their contralateral limbs. This reflects the considerable difficulty with the

“carry-over” of training effects that is commonly recognized by rehabilitation therapists—the failure to learn to compensate spontaneously for impairments that can be overcome by verbal cuing from the therapist. This disturbance, one of the most bewildering and frustrating in brain injury, partly underlies the great desire by clinical investigators to improve treatments for neglect. The basis for this paradoxical awareness has not been well investigated. It does not appear to be consequent to generally decreased motivation or initiation, since some patients spontaneously report their neglect and avidly perform tasks on their ipsilateral side. The disorder also does not appear to be a form of “anosodiaphoria,” the emotional indifference to a pathologic condition (129, 130), since some patients with neglect express concern for their inability to accomplish tasks successfully (111), even though they may not emotionally intone their voices. Instead, the difficulty appears in part to reflect a lack of “mindfulness” for their spatial impairment during task performance. That is, such patients do not remain continuously aware of their limitations and make corrective adjustments, and as a result they recurrently encounter difficulty during daily living tasks due to spatial inattention (e.g., failing to protect the hemiparetic limb from injury during transfers from bed to chair) unless they are cued. This suggests a deficit of what is termed “working memory” (the active maintenance of a fact in mind for immediate use when needed). But this is not the complete explanation, because even when neglect patients become frustrated because of their neglect on tasks, such as failing to propel a wheelchair through a narrow doorway due to collision on the neglected side, it is often hard for them to efficiently resolve the problem (111). This suggests that neglect is a very powerful disorder that resists self-initiated problem solving, even when patients understand that they have difficulty and thus, in principle, should be able to overcome the problem.

An example of the complexity of problem solving in neglect was shown in a study by Mark *et al.* (131). Patients with neglect improved their cancellation when they were instructed to *erase* stimuli rather than mark them. Nonetheless, some patients could not completely overcome their neglect. This suggests that unilateral neglect involves multiple concurrent cognitive impairments, such that some are more easily overcome than others. A vivid example of this was also shown by Mesulam (10), who found that monetary payment for every canceled stimulus improved neglect in a patient, but again did not abolish it. Alternatively, these examples might reflect the existence of a spatial “gradient” to neglect, such that problem solving becomes more difficult the farther that the problem occurs in the contralateral direction. Perhaps on functional tasks, despite understanding their disorder and benefiting to some extent from changes in problem solving strategy, patients with neglect may simply be unable to orient sufficiently contralaterally, at least through self-initiation. Cantagallo and Della Sala (111) reported that the famed film director Federico Fellini, whom they evaluated after his stroke, understood that he omitted marking targets during cancellation but nonetheless seemed powerless to improve his performance on his own. The observations suggested

Functional neglect

that Fellini was aware of stimuli to his left, in the same way that neglect patients who confabulate the left sides of words that they read aloud are responding to incompletely detected stimuli. Numerous other examples of “covert awareness” in neurologic disorders have been described, such as the changes in electrical skin conductance that occur when brain-injured patients are shown familiar faces that they nonetheless cannot recognize overtly (132). A great mystery in cognitive research is why awareness for environmental stimuli is sometimes incomplete following brain injury.

However, most patients recover substantially from neglect, if not completely, and typically within a few months (27, 28, 33, 38, 39, 42, 121, 133-136). The recovery can be highly erratic, marked by day-to-day fluctuations (137), despite general improvement over several months. Unfortunately, inconsistency in the kinds of tests used for neglect has prevented understanding its prevalence, particularly in the chronic state (138). Consequently, the urgency for treating acute neglect is unclear. Such intervention might curtail particularly disabling outcomes, such as falls, collisions, or painful dystonia, but the incidence of these complications is also unknown. Thus, it is not clear whether neglect rehabilitation deserves priority over therapy for other impairments that may occur with chronic stroke, such as aphasia or hemiparesis. This understanding becomes particularly important if financial resources for rehabilitation become strained, which may occur as the population of stroke survivors increases.

Attempts to describe “recovery” must acknowledge that the ability to detect neglect depends in large part not only on the sensitivity of the individual tests used, but also on the overall processing demands or stresses that the individual must confront while being tested, or the facilitating effect from certain activities. Thus, for example, neglect severity can change with changes in gaze direction (139, 140) or with limb movement (141). More pertinent to clinical practice is that neglect that has completely recovered long after stroke onset can be reinstated by intravenous benzodiazepine (142). These observations emphasize the “state-dependency” of cognitive disorders following structural brain injury, that is, their dependence on the total cognitive processing resources available. In practical terms, judging whether an individual has recovered from neglect may depend on diverse factors such as the person’s overall health, concurrent medications, or whether the person ruminates over miscellaneous concerns at the time of testing. These factors are difficult to control. However, estimating an individual’s current cognitive performance level may be improved through repeated assessment over several days (if there is no indication that the person’s health is declining), as suggested by the observations reported above by Small and Ellis (137).

Finally, despite the close association between acute unilateral neglect and functional recovery, it is still unclear to what extent neglect directly impairs function. Clearly, as shown by the accounts and illustrations in the preceding section, neglect can be functionally disruptive. But to what extent does functional recovery *depend* on

neglect vs. other disorders? Despite the plethora of studies on functional outcomes and acute cognitive status, we do not well understand the relative contributions of other disorders such as aphasia, depression, and so on. We will probably not have such understanding until the full complement of cognitive disorders that follows brain injury is consistently and sensitively assessed in a large acute stroke population. This is unlikely in the near future, given the lack of standard comprehensive assessments for many of these disorders.

Some evidence suggests that unilateral neglect may not directly affect chronic functional status. Kinsella and Ford (33) found that acute neglect patients had impaired functional status at 18 months compared to stroke patients without acute neglect. However, the chronic disability in the acute neglect group was not strictly related to *concurrent* neglect, because only half of the acute neglect patients had measurable neglect at follow-up. On the other hand, Cherney *et al.* (143) failed to find a significant difference in functional status at 3 months between patients with and without acute neglect. However, the patients with acute neglect had longer hospital stays than did stroke patients without acute neglect. Thus, the absence of differences between groups at 3 months may have been due to differences in the amount of rehabilitation they received.

Other studies have failed to significantly associate acute neglect with functional status when compared with other acute cognitive disorders. Unfortunately, there has been no consensus on what disorders are more important to outcomes. Thus, Sundet *et al.* (61) found that neglect correlated with chronic functional status, but not as strongly as did acute apraxia and pathological laughter or crying (emotional lability). Similarly, Mysiw *et al.* (60) found that unilateral neglect was not as successful as impaired attention, calculation, and judgement for predicting functional status at hospital discharge. Gialanella and Mattioli (56) and Pedersen *et al.* (55, 144) found that neglect did not predict outcome functional status, in contrast to anosognosia for hemiparesis. Blanc-Garin (57) observed that cancellation tests did predict functional recovery in stroke patients, but without relation to the laterality of omissions on these tests. This suggested that non-spatial inattention was crucial. This observation is consonant with Hjaltason *et al.* (127), who noted that patients who were aware of their chronic neglect were also impaired in sustained, non-lateralized attention. Similarly, Samuelsson *et al.* (135) in a longitudinal study found that perseverations (needlessly repeated actions) on cancellation tests correlated with acute neglect, but that these persisted even when neglect had become less strongly asymmetric 6-7 months later.

Non-lateralized alerting may benefit neglect (11-13), which is consistent with other evidence that suggests that the attentional deficit in neglect is not strictly unilateral (145, 146). Reviewing this evidence, Robertson (147) suggests that unilateral neglect is fundamentally a disorder of non-lateralized attentional capacity. While Hjaltason *et al.* (127) indicated that the attentional deficit in neglect may

at least affect sustained attention, experimental studies have not otherwise examined whether other components of attention [e.g., selective attention, divided attention (148)] are also impaired in a non-lateralized manner in patients with unilateral neglect. Nonetheless, Robertson's proposal could help account for changes in spatial inattention during recovery from focal brain injury. Acute focal hemispheric injury sufficient to disrupt general attention would be associated with unilateral spatial neglect, due to a sudden imbalance between the mutually opposing, contralateral attentional biases of the cerebral hemispheres, according to one hypothesis (149). Recovery would then attenuate unilateral neglect, perhaps due to functional cortical reorganization or compensation from undamaged regions (150, 151), while non-spatial inattention would persist because it is less amenable to compensation. General inattention would therefore be prominent during the chronic phase of illness following focal brain injury, rather than unilateral spatial neglect. The observation that unilateral neglect is more frequent, severe, and enduring following right than left hemispheric lesions (39) is consistent with evidence suggesting that primarily the right hemisphere mediates general alerting and sustained attention (152-154). These observations link unilateral spatial neglect with general inattention.

6. THE FUNCTIONALLY VALID ASSESSMENT OF NEGLECT

While much work remains concerning the relative importance of unilateral neglect to functional outcomes, the neglect assessments that predict functional status and recovery have been well established. Essentially, the cancellation test has most often been found to be successful (27, 31, 32, 72, 91, 92, 121, 155-157). This test presents numerous distinct images across a page. The subject must mark all the occurrences of a particular image (e.g., the letter "A") and disregard all other images (non-targets) if present. (The activity is akin to canceling a parcel that has numerous postage stamps; one must mark only the stamps and not other printed items.) Some versions require speeded performance, so that the subject must mark all targets in a restricted time interval. However, neglect may be found simply by having the patient work at a self-determined pace and indicate when he or she has completed marking the page. Neglect is scored by counting the number of unmarked targets after test completion. Some investigators recommend measuring the imbalance in target omissions between the right and left sides (155, 158, 159) to indicate the extent to which the neglect is actually unilateral. The value of the cancellation test comes not only from its correlation with functional status and outcome, but also because it can be cheaply and rapidly reproduced, either by photocopying a standard version or, in a pinch, sketching out an example on hospital chart paper if necessary. Different cancellation test versions have been published, but unfortunately there is no consensus for which version is most sensitive to neglect or functional outcomes.

The preeminence of cancellation tests for predicting functional outcomes is plausible. Cancellation

tests typically measure visual search over a cluttered array, which in this regard is similar to common encounters with the real world, where one must search for salient items among undesired objects from a crowded table top, dresser drawer, kitchen shelf, or roadway. In contrast, other neglect assessments such as line bisection, reading, copying, and drawing from memory assess functions that are less frequently used during daily living activities in general.

The Behavioural Inattention Test, or BIT (160-162), has emerged as the internationally favored comprehensive assessment for unilateral neglect. It was developed in part to include "ecologically valid" simulations of actual daily living activities on which one may find unilateral spatial bias. One part of the battery includes traditional pen-and-paper neglect assessments (different varieties of cancellation tests, line bisection, figure copying), and the other part comprises the ecological portion, which includes activities such as inspecting a picture of a life-sized plate of salad, reading from a menu, and sorting familiar coins. The complete battery has been found to correlate well with occupational therapists' judgements on the occurrence of unilateral neglect on functional tasks (27, 162). However, administering the complete assessment is time consuming, probably all the more so for patients with marked neglect, who tend to accomplish tasks very slowly and may require repeated prompting. Thus, fatigue may supervene; subjects may be unable to complete the test at one sitting. More important, studies have shown that the traditional pen-and-paper tests in the BIT are sufficient to detect most instances of neglect (156, 162, 163), and that a single cancellation test from the BIT may correlate with functional status or recovery (27, 121). Therefore, for most purposes cancellation tests by themselves are adequate for predicting functional status.

However, cancellation tests and other activities assessed by the BIT concern only *extrapersonal neglect*, that is, unilateral inattention to the environment separate from the body. Many brain-injured patients show unilateral neglect for their own bodies, as demonstrated above. Such "personal" neglect may occur independently of extrapersonal neglect (102, 164-169). Unfortunately, the assessment of personal neglect has not been as well developed. One detailed test of personal neglect involves counting the number of limb movements made on the left vs. right side of the body during commanded self-grooming (combing, shaving, or make-up application) over 30 seconds (168). The test is reported to be highly reliable and sensitive to neglect. However, this test is not helpful for several reasons: (1) The validity of performance to command for real life behaviors on these tasks has not been evaluated. (2) The lateral differences in movements for these tasks may be influenced by factors other than neglect, such as the location of the part in the scalp, premorbid laterality biases in action sequences (e.g., habitually starting on the right or left), and the fact that a movement that commences on one side of the face or scalp may continue over to the other side, thus leaving less work to do on that side. (3) The laterality of movements close to the midline are difficult to judge. (4) Some patients move so quickly as to challenge accurate counting, even when the behavior has been video taped (author's observations).

Functional neglect

An alternate test of personal neglect is the “fluff test” (170), which involves attaching multiple adhesive pieces of cardboard to the patient’s clothing while he or she is blindfolded. Afterward, the blindfold is removed and the patient is asked to detach all of the cardboard pieces, akin to picking lint from clothing. The proportion of cardboard pieces removed from the total applied is calculated. The test is difficult due to the need to prepare the stimuli and because the patient must wear clothing suitable to assure stimulus adherence. Furthermore, the correlation of any tests of personal neglect for functional outcomes has not been evaluated, and so their practical value for neurologic rehabilitation is undetermined.

Finally, the assessment of motor neglect has been even less well developed. Most reports have used informal observations. Some inconsistency in the definition of motor neglect has been noted (171). Only one formal assessment battery for motor neglect has been developed (172). However, this approach assesses diverse behaviors, including spontaneous limb use under uncontrolled circumstances, movement of the hand into ipsilateral or contralateral space to command (which actually assesses directional hypokinesia (173) or motor intentional neglect (174), not motor neglect itself), and vaguely described spontaneous behavior during postural supporting activities or when touching painful stimuli (!). These observations are collapsed to a single 3-step ordinal scale of undetermined reliability or validity. For these reasons this scale cannot be recommended.

A promising alternative assessment to motor neglect comes from research on constraint-induced movement therapy (CI therapy) for improving learned nonuse after stroke (82). One assessment for learned nonuse is the Actual Amount of Use Test (AAUT), a preliminary description of which is provided by Uswatte and Taub (175). Patients are discreetly video taped in the laboratory while they are asked to perform certain tasks that are posed to help their participation with therapy, such as filling out a form, tucking an appointment card into a wallet, inserting a cassette into a VCR to observe playback of their treatment responses, and so on. The AAUT is ethically permissible because patients consent to video recording during the therapy, but without being told what specific interactions with investigators will be recorded. The patients are not cued to use a particular hand during the AAUT. Subsequently, raters view the tape recordings and score the relative amount of use by the contralateral hand on each of the tasks. The authors indicate that the predictive value of the AAUT for real-world functional tasks has so far not been assessed. This test nonetheless offers a controlled basis for evaluating motor neglect as well. Research is needed to decide whether the AAUT could be practical for predicting the functional implications of motor neglect. Another assessment of learned nonuse is the Motor Activity Log, or MAL (175), which relies on self or caregiver reports of relative contralateral limb use on multiple routine daily living activities. Although the assessment is subjective, high interrater reliability has been reported between caregivers and patients, at least when participants had been screened for cognitive disorders. The

MAL may therefore offer a more feasible assessment of motor neglect, but thus far motor neglect has not been experimentally evaluated with the MAL.

7. REHABILITATION OF NEGLECT

The treatment of unilateral neglect in clinical practice is not theoretically based (176). Instead, treatment is guided by observations of the patient’s performance on standard basic daily living activities, and then training is implemented to improve attention and action toward the contralateral side, according to the specific tasks that were impaired (177). Perhaps as a result, treatment approaches to neglect in clinical practice are not consistent. Occupational therapists sometimes place a highly attractive stimulus such as a stripe in contralateral space (“anchoring”) to overcome scanning biases, or they teach patients to use their finger to guide themselves contralaterally (19, 178-180). Some individual patients have been observed to learn to apply and benefit from these interventions. However, systematic studies on the efficacy of these approaches have not been conducted.

Over the past 40 years various experimental treatments have been introduced to treat neglect. Initial attempts were based on behavioral training, including providing feedback during errors or practicing contralateral scanning, which usually improved neglect. Nonetheless, these attempts either inadequately (or not at all) assessed control subjects or did not assess whether treatment effects transferred to other daily living activities (178, 181-188). Other studies failed to find consistent transfer of treatment effects to other tasks (189-191) or any benefit at all from specific treatment for neglect (192, 193). The placement of objects to be used for daily living activities in either the contralateral or ipsilateral side of space does not affect recovery of functional activities in patients with neglect (194). An exceptional study was by Young *et al.* (195), who found that training acute stroke patients on the Block Design subtest from the Wechsler Adult Intelligence Scale improved reading contralateral words. Nonetheless, such training has not become routine. A limitation of these behavioral or environmental treatment approaches is that they were not developed from theoretical models of disability, but rather from observation and trial-and-error. This has complicated interpreting the basis for treatment failures (196), or, for that matter, successes. For example, it is unclear why practice on Block Design should benefit unilateral neglect.

In contrast to the foregoing studies, Antonucci *et al.* (197) reported that comprehensive scanning training and prolonged practice with reading, copying, and describing pictures resulted in significant improvement on standard and functional aspects (102) of unilateral neglect that had not been directly trained. They thus provided evidence for transfer of training effects. Furthermore, the interval since stroke onset was unrelated to neglect improvement. Antonucci *et al.* suggested that the basis for their successful behavioral intervention was “massive stimulation,” since training sessions were one hour daily, five days a week, for eight consecutive weeks, or 40 hours total. In contrast,

Functional neglect

earlier studies used more limited treatments. Thus, in a manner similar to that of the “massed practice” of CI therapy for chronic stroke hemiparesis (82) that was referred to in section 6 above, transfer of training effects following cerebral injury may only occur after a critical amount of task practice has been given. In the case of therapy for neglect, Antonucci *et al.* suggested that massive stimulation promotes improved awareness for the deficit. However, their hypothesis was only inferential rather than based on debriefing the treated patients. Alternatively, perhaps massed stimulation for neglect results in functional reorganization of cerebral areas involved with directional spatial attention, independent of any awareness for neglect. Functional neuroimaging studies from CI therapy programs for chronic hemiparesis support the occurrence of cortical reorganization following massed motor practice (198). Since participants with major cognitive disorders have been excluded from CI therapy trials thus far, it does not appear that improved awareness for motor deficits is obligatory for therapeutic benefit. Correspondingly, neglect may respond to massed stimulation because of unconscious learning. Unfortunately, Antonucci *et al.* did not indicate the duration of training benefits, nor did they state whether benefits transferred to daily living activities in the real world, in contrast to the findings in support of CI therapy benefits.

Numerous other interventions have used more intimate or even invasive contact with the patient. No particular treatment approach has proven popular in clinical practice. A comprehensive overview of these diverse approaches has recently been provided elsewhere (199). A few of the more frequently assessed treatments are presented below.

7.1. Vestibular stimulation

In 1941 Silberpfennig (14) discovered that a standard clinical assessment of brainstem function, the flushing of one ear canal with cold water to induce nystagmus (reflex lateral drifting of the eyes in unison), could improve contralateral reading and reaching, as well as torticollis, in patients with neglect. This effect, known as “caloric stimulation,” was repeatedly confirmed decades later (200-203). The improvement of left neglect generally occurs when the left ear is treated. The basis for this improvement is unclear but is considered not to reflect nonspecific arousal from ice water, since the benefit is specific to treating only the left ear. Unfortunately, with rare exceptions, treatment benefits last only 15 minutes, and therefore this fascinating phenomenon has no practical value. A related effect has been shown by exposing the patient to opticokinetic stimulation, which also induces nystagmus (204-206). This effect is induced by having the patient view a rapidly rotating vertical cylinder painted with alternating black and white wide vertical stripes, which causes a horizontal beating of the eyes akin to the effect of watching telephone poles rapidly go by while looking from the window of a speeding train. As with caloric stimulation, the basis for the improvement is unknown, and the benefit is short-lived.

7.2. Eye patching

Butter and Kirsch (207) in 1992 observed that occluding the right eye with a patch resulted in modest

improvement in line bisection or cancellation tests. In contrast to the behavioral modifications in scanning described above, Butter and Kirsch’s approach was developed from basic neuroscience principles. The hypothesized basis for the benefit was the predominantly contralateral retinal input to the superior colliculus, a small paired brainstem structure that is considered to be important to eye movement control. Experimental observations in lesioned laboratory animals had suggested that the twin superior colliculi mutually inhibit each other, while each one individually excites the ipsilateral cerebral cortex. Asymmetric cortical activation should result in increased contralateral attention (149). Thus, right-sided eye patching should diminish the activity of the left superior colliculus. This in turn would disinhibit the right superior colliculus, which would then activate the lesioned right hemisphere in patients with left neglect. Consequently, increased left visual exploration should emerge from right eye patching in left neglect patients.

Unfortunately, the remediation of neglect through eye patching has not been as straightforward as one would have hoped. First, the anatomical relationship between the eyes and the superior colliculi is unclear. Previc (208) indicates that while the input to the superior colliculus is primarily from the contralateral retina in *most* mammals, in primates the inputs are more bilateral. Second, subsequent studies of eye patching were inconsistent. Barrett *et al.* (209) found that right eye patching aggravated left neglect in a case study, while left eye patching improved neglect. In a subsequent case report, Barrett *et al.* (210) replicated the results of Butter and Kirsch, that is, benefit from right eye patching, but not left, at least on a cancellation test. Because so few subjects have been evaluated, it is premature to postulate how monocular patching affects neglect. Intraindividual differences may be due in part to differences in the innervation of the superior colliculi from the eyes, or differences in neglect subtypes. More important, however, is the conclusion that monocular patching may exacerbate neglect (209). This observation may have practical importance, since patients may need to wear patches for other reasons, including isolated cranial neuropathy or corneal injury. The effect of patching on functional activities has not been determined.

7.3. Pharmacologic intervention

Following experimental studies in laboratory animals, in 1987 Fleet and Heilman (211) reported that a medication commonly used to treat Parkinson disease, bromocriptine, could improve unilateral neglect on standard tests in two stroke patients. Anecdotally, one of the patients benefited on functional activities also. Compatible observations were reported in a later case study with bromocriptine (212) and a series study using another antiparkinsonian agent, carbidopa with levodopa (Sinemet) (213). However, it is unclear why a systemically distributed drug should benefit unilateral neglect, since one would expect drug receptors in both cerebral hemispheres to be stimulated. Indeed, a straightforward explanation is complicated by reports that bromocriptine may aggravate unilateral neglect (174, 214). As with eye patching, too few patients have been treated to provide generalizations, and

Functional neglect

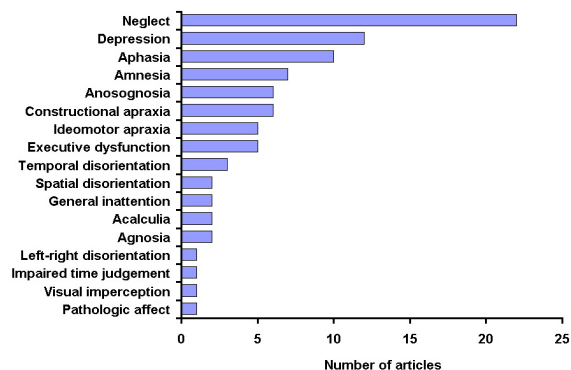


Figure 6. A representation of the significance of unilateral neglect among contemporary investigations for cognitive disorders that follow stroke. The bars indicate the number of articles that assessed the specific cognitive disorders listed from all of the citations shown in table 1.

the functional responses to treatment have not been well evaluated.

7.4. Prisms

A recently developed approach reportedly has the advantages of simplicity, persisting benefit, and transfer of training effects. This method uses prismatic lenses that shift the field of view 10° ipsilaterally. The treatment program pioneered by Frassinetti *et al.* (215), termed prismatic adaptation (PA), involves 20-minute sessions twice a day for 2 weeks. During the sessions, patients wear the lenses and repeatedly point with the ipsilateral hand to the location of stimuli that occur at pseudorandom locations at arm's length. According to Frassinetti *et al.*, PA resulted in significant improvements on subtests from the BIT, a reading test, and pointing to objects in the extrapersonal environment to command, in contrast to control subjects with neglect who did not wear the prisms. There was no significant benefit to personal neglect as assessed by the fluff test, although there was a trend in this direction. However, few patients had personal neglect, so there may have not been sufficient power to detect a treatment effect. Preliminary findings suggested that treatment effects were maintained for as much as 17 weeks. Furthermore, neglect progressively declined during several weeks of follow-up, suggesting that the PA treatment had somehow facilitated active recovery long after the treatment itself had concluded. Using an abbreviated form of the same treatment, Farnè *et al.* (216) found that one patient improved in exploring rooms in the home. Further studies are needed to determine whether patients significantly improve on standard functional activities assessments following PA therapy.

Frassinetti *et al.* (215) emphasize that one reason for the success of PA is that it relies on “bottom-up” training, that is, through the passive modification of sensory input rather than depending entirely on active gaze shifting to alter views of the environment, as has occurred on “top-down” neglect training tasks such as visual tracking of kinetic stimuli. The latter require patients to be fundamentally cognizant of their disorder, which as we have seen is not always the case. Correspondingly, “top-

down” training may not transfer to untrained activities. In contrast, Frassinetti *et al.* suggest that PA may improve spontaneous contralateral scanning, which in turn may improve the internal mapping of the surrounding environment. This may stimulate further exploration contralaterally. Eye movement analyses could test this hypothesis.

The PA method uses simple equipment and does not require much skill to train. The procedure is well tolerated. If further studies support enduring benefits to daily living activities, then PA may become a useful treatment for unilateral neglect.

8. DISCUSSION

Unilateral neglect is a conundrum for neurologic rehabilitation. It is commonly encountered in acute rehabilitation programs and obviously appears to impair a wide variety of daily living activities. Furthermore, rehabilitation therapists commonly regard unilateral neglect as one of the most vexing disorders to follow brain injury, due to the common difficulty with the carry-over of training effects from day to day. Frequently, patients with neglect lack insight and understanding for their disabilities. Many studies indicate that acute neglect forecasts poor recovery of functional independence. For these reasons unilateral neglect would appear to be of utmost importance in trials to improve rehabilitation outcomes.

On the other hand, many studies indicate that neglect usually recovers several months following brain injury. In contrast, as much as 50% of chronic stroke patients remain functionally impaired and have associated cognitive decline (217), even though unilateral neglect is not an obvious part of their presentation. Therefore, is it worthwhile to treat acute unilateral neglect? At this time there are insufficient data to answer. Points raised in this article could help to reconsider the significance of unilateral neglect in relation to functional activities and the design of rehabilitation research for cognitive disorders following brain injury.

As we have seen, unilateral neglect commands widespread interest in the treatment of brain injury patients, particularly following stroke (table 1). Using a ballot-counting measure again, figure 6 indicates the frequency of cognitive disorders that were evaluated in the studies from table 1. The leading disorders were unilateral neglect, depression, and aphasia. [Whether depression should be considered a “cognitive” disorder may be debated, but there are well established links between depression and other kinds of cognitive decline (218-221).] This suggests that the cognitive disorders that are targeted for outcomes studies in stroke are those that have well established manners of evaluation, e.g., the BIT or individual cancellation tests, the Zung Depression Scale, and the Western Aphasia Battery. In contrast, the remaining disorders either do not have well established evaluations (e.g., anosognosia, pathologic laughter and crying) or are not emphasized in stroke research (e.g., executive dysfunction, memory disorders). Some of these disorders

are assessed by laborious tests, such as reaction time tasks when assessing general attention or the Wisconsin Card Sorting Test when assessing executive processes. Also, the cognitive disorders that are most commonly evaluated in outcomes studies in stroke are linked with lateralized cortical injury. This bias is probably a consequence of cognitive research on stroke in general, which favors neglect and aphasia. Regardless of the reason, the emphasis on cognitive assessments that are traditionally or most conveniently administered for stroke may divert attention from other disturbances that could also seriously affect functional outcomes.

In contrast to stroke studies, clinical neuroscience investigations of other populations (e.g., dementia, aging, schizophrenia) emphasize disorders that are less strongly lateralized, such as executive dysfunction and general inattention. Such disorders have been frequently associated with impaired functional status. For example, the Useful Field of View test (UFOV), a measure of divided attention, and the Trail Making Test B, a measure of executive function (controlled alternating responses in this case), predict impaired driving and skills for living alone in the elderly (222-224). Disturbances of executive function, general attention, and memory follow stroke as well (11, 60, 63, 225). Furthermore, studies of patients with chronic vascular disease, which do not strictly include stroke, also indicate significant non-lateralized cognitive impairments (226). The neuropathologic changes that occur in such patients would likely occur in stroke patients as well. Unfortunately, the apparent bias against evaluating such disorders after stroke limits understanding their relative contribution to functional decline following stroke. This lacuna in knowledge would be remedied by assessing stroke patients on more diverse cognitive assessment batteries and relating these findings to functional recovery. From such evaluations we would have a better understanding of the relative importance of unilateral neglect.

Another unresolved issue is understanding how exactly does neglect affect functional tasks. We saw above the many ways that neglect *can* interfere with daily living activities, but we do not yet understand the *consistency* of unilateral neglect during daily living activities. Much more detailed observation are needed. In addition, we have yet to understand how well unilateral neglect explains the variance in functional activities assessments such as the Functional Independence Measure (FIM) (227) or the Barthel Index (228) (the two leading assessments of basic daily living skills), or assessment tools for instrumental activities of daily living such as the Frenchay Activities Index (229), the Lawton-Brody assessment (230), or the Older American Resources and Services assessment (OARS) (231). It is possible that other disorders, such as executive dysfunction, correlate better with such instruments. If this were found to be the case, then much more emphasis should be placed on understanding the natural course of recovery from these disorders and what treatments for them are effective.

Through most of the past several decades, unilateral neglect has been refractory to standard or

experimental therapy. However, the findings by Frassinetti *et al.* (215) and Farnè *et al.* (216) suggest that the benefits from treating neglect may extend well beyond the tasks that were directly trained and may be long lasting. A valuable inquiry then would be to find out whether early treatment of neglect, before its spontaneous recovery, would have any bearing on functional status in chronic stroke. Although unilateral neglect may fundamentally be a disturbance of general attention, which normally may persist longer than neglect, the finding that PA therapy is followed by continued improvement of unilateral neglect over several weeks suggests that it could be improving general aspects of attention, and not only spatial bias. Further research should evaluate whether PA or other methods' treatment benefits extend to non-spatial tasks. If this were to be shown, then such treatments might offer inexpensive or convenient ways to treat diverse disorders.

In conclusion, unilateral neglect remains a fascinating and common disorder. Improved understanding of its relative importance toward functional recovery following acute brain injury would do much to improve our general understanding of mechanisms of response to brain injury and adaptation.

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Functional neglect

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