Using Reaction Time to Assess Patients With Unilateral Neglect and Extinction

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ABSTRACT

Brain damage often results in visual defects and/or higher order visuo-spatial disorders including the syndromes of unilateral neglect and extinction. These syndromes and their associated behavioral sequelae are described along with several standard assessments and methods for behaviorally quantifying such deficits. In particular, the advantages of the reaction time measures commonly used by cognitive neuroscientists are surveyed. In order to illustrate how reaction time measures can be used to examine the subtleties of visuo-spatial deficits, several reaction time studies that have been conducted in patients with neglect and/or extinction are discussed. These studies stand as an example of how reaction time measures can contribute to both clinical and experimental neuropsychology.

A substantial number of patients suffering from unilateral brain injury will experience hemianopsia, or contralesional visual field defects, which stroke representing the most common cause (Zihl, 2000). Higher order visual and attentional disorders are also common following unilateral brain damage, sometimes co-occurring in combination with primary visual field defects. However, visuo-spatial and attentional deficits are often overshadowed or masked by primary sensory deficits or other problems such as aphasia, monoparesis or hemiparesis, affective changes, and memory impairments, to name a few. Although brain damaged patients are now generally referred for physical therapy, speech therapy, and occupational therapy as deemed necessary, rehabilitation targeting specific visual and attentional deficits has lagged in development (although see Robertson & Halligan, 1999; Robertson, Halligan, & Marsh, 1993).

Some might argue that visual rehabilitation protocols are unnecessary due to high levels of spontaneous recovery. While it is true that patients suffering from primary sensory damage can often compensate for their deficits via appropriate eye and head movements, estimates of the percentage of hemianopic patients that exhibit spontaneous visual recovery have only ranged between 12 and 30% (see Chapter 2, Zihl, 2000). In contrast, two recent studies by Kasten and colleagues have shown that 1 hr of visual field training per day over a 6-month period in patients with visual field defects resulted in significant enlargements of the visual field, as tested via conventional perimetry, as well as some benefits in color and form recognition (Kasten, Poggel, & Sabel, 2000; Kasten, Wuest, Behrens-Bamann, & Sabel, 1998). Nonetheless, a substantial number of stroke patients suffer from cortical damage that compromises higher order visual and attentional abilities as well, particularly when the right hemisphere is affected (De Renzi, 1982; Posner, Walker, Friedrich, & Rafał, 1984; Robertson & Rafał, 2000; Zihl, 2000). Primary examples of

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higher order visual deficits include the syndromes of unilateral neglect and extinction. The extent and degree of spontaneous recovery from these types of visual spatial deficits is neither well documented nor agreed upon (see Robertson, Halligan, & Marshall, 1993).

In most, but not all, cases of unilateral neglect, the acute profile of a complete lack of awareness of contralesional stimuli can gradually recover. Even in instances where recovery is thought to be complete, sensitive testing has revealed differences in processing contra- versus ipsilesional stimuli. For example, neglect often evolves into extinction such that patients become capable of detecting contralesional stimuli that are presented alone but not when a competing stimulus is simultaneously presented in the patient's ipsilesional, or intact, visual field. In this case, the patient no longer “neglects” the presence of a single item in the contralesional side of space, but he/she may extinguish and be unaware of its presence under conditions of double simultaneous stimulation (DSS). Such behavior is often referred to as extinction because the competing ipsilesional stimulus appears to extinguish the contralesional stimulus.

Moreover, even when patients have recovered their ability to detect contralesional stimuli under DSS, they cannot always do so with the same speed or reliability as in the opposite visual field. Given that quick and efficient processing of stimuli in the space that surrounds us is important for many day-to-day activities such as driving, finding groceries on store shelves, searching for keys, cooking meals, and so forth, sensitive methods for quantifying visuo-spatial abilities can be crucial to patient diagnosis and follow-up care. For the experimental neuropsychologist, patients exhibiting such marked differences in visual processing on one side of space versus the other offer a unique opportunity for investigating the way that space is represented in the brain as well as the neural structures involved in attending to or acting upon such spatial representations.

Typical methods for assessing unilateral neglect and/or extinction have relied on traditional bedside exams and paper and pencil tests, such as Albert’s Line Cancellation test, line bisection tasks, and picture copying or clock drawing (Albert, 1973; Marshall & Halligan, 1993; Robertson & Halligan, 1999). The advantages of such tasks are their utility; they can be administered quickly and easily at the patient’s bedside and they are sufficient for diagnosing the more severe cases. However, the limitations of such tests are numerous. First, there is the issue of limited samples. In many pencil-paper tasks, the patient is asked to copy or draw a picture from memory. Occasionally, patients may be asked to draw or copy several pictures, but this can become quite time-consuming and tiring for the patient as well. Establishing whether a patient has neglect is therefore sometimes made on the basis of only one or two drawings. In this case, it is the reliability with which the patient can be expected to neglect contralesional stimuli that cannot be estimated.

Second, many standard assessments of neglect use unlimited exposure time. For example, in standard line cancellation or letter search tasks (Fig. 1), patients are typically allowed as much time as needed to cross out all the lines on the

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**Fig. 1.** Schematic examples of two standard bedside tests for neglect. Line Cancellation tasks require patients to cross out or “cancel” all of the lines on the page. Letter or Symbol Search tasks require patients to find and circle all of the targets, the letter A in this case. Such tests are typically presented on paper in a self-terminating fashion.
page or to find and circle all the A’s, respectively. As many clinicians and experimenters are sure to have observed, some patients will initially neglect several contralesional items, but later find them as they continue to search or re-check their work. Thus, two clinically different patients could in fact receive the same test score because a patient with mild neglect may only miss one or two contralesional items, while a patient with severe neglect may eventually find all but one or two of the target items after repeated searching. Such differences are obvious to the person administering the test, but the numerical scores on such tests are not generally comparable across patients or even across test sessions within the same patient. In this case, it is the severity of neglect that becomes difficult to quantify. In the absence of limited exposure durations and/or limits on the time allotted for patients to respond, such tests can also be challenged on the basis of their sensitivity. A patient who shows no signs of neglect on standard drawing and copying tasks, may show large behavioral differences in responding to contra-versus ipsilesional stimuli when confronted with time-limited displays.

A further drawback of pen and pencil type assessments is their inability to capture the attentional search strategies employed by particular patients. In one case, a patient with left visual neglect may seem to systematically search the page from right to left, first responding to the salient right-sided targets and gradually progressing toward the left (albeit not completely). Another patient with left neglect may search the page just as systematically but by beginning near the center of the page and progressing rightward. Still another patient may search for targets randomly, haphazardly spending unequal amounts of time in various portions of the stimulus display (presumably allocating the least amount of time to the neglected side). By carefully examining differences in patients’ search strategies, clinicians and experimenters can assess whether a patient’s attention is pathologically drawn to one side of space and the degree to which patients are able to strategically allocate their attention in the face of such visuo-spatial deficits.

A final limitation of bedside exams is that it can be quite difficult to monitor or control a patient’s point of visual fixation. It is both clinically and experimentally relevant whether a right hemisphere patient neglects stimuli falling only on one side of the retina as opposed to the left side of an object (irrespective of its placement in the visual field), one’s own body midline, some other salient axis, or some combination of all the above. At one level, such information is important for distinguishing visual field defects from higher order spatial deficits. At another level, such distinctions capture variations in the essence and pervasiveness of the disorder. In other words, we can now consider the particular spatial representations in the brain that are being affected (e.g., viewer-centered, environment-centered, object-centered, scene-based, etc.). Portable laptop computers have made it increasingly easy to administer computerized versions of standard assessments of neglect, to control the timing of stimulus presentation, and to collect various reaction time (RT) measures, even at bedside. The advantages of computerized presentations and RT measures are numerous. First, stimulus presentation durations and the time allotted for response can be carefully controlled. Of particular relevance for patients with unilateral neglect is the fact that very brief stimulus durations can be used. Limitations in the speed with which humans can move their eyes (approximately 150 ms) ensure that test stimuli cannot be foveated if participants are required to fixate/monitor a central marker while test stimuli are presented in the periphery for durations of 150 ms or less. The ability to concurrently control stimulus presentation rates and monitor visual fixation therefore results in tests with greater sensitivity to differences in visual processing between the two visual hemifields (or between two sides of an individual object). Furthermore, the ability to titrate stimulus presentation rates as a patient’s performance improves also offers a means for tracking recovery in such populations.

A second advantage of computerized RT measures is that various stimuli or trial types can be easily randomized. If desired, a new random sequence can be generated each time the patient performs the task, attenuating some potential carry over effects from one test session to another. In addition to obtaining accuracy data,
which is typically scored on an all-or-none basis, continuous reaction time measures can also be obtained. This provides a way to numerically quantify a patient’s performance via means, medians, and estimates of variability over trials and allows performance in various conditions to be statistically compared (e.g., left vs. right visual field stimulation). Note that in neglect patients in particular, each patient can serve as his/her own control, as the variable of interest is usually performance in the neglected visual field (or side of an object) versus performance in the opposite, intact field.

Now that CT or MRI scans are commonly used in the diagnosis and treatment of patients suffering from strokes, the greater sensitivity and quantification abilities inherent in RT studies convey an additional benefit. Clinical cases of neglect often involve a constellation of deficits including spatial biases in perception, motor function, mental imagery, and memory. As different aspects of neglect become better characterized and dissociated via sensitive RT measures, differences in the severity and/or type of neglect that manifests in one patient versus another can be correlated with neuroanatomical differences in lesion sites. By using the lesion overlap method, neuroanatomical images of the lesions for a number of patients who exhibit a similar behavioral profile can be compared such that lesioned areas that are commonly affected across patients can be distinguished from other tissue damage that may not be directly involved in the deficits associated with visual neglect. Such structural analysis of the “regions of greatest overlap” among brain lesioned patients who exhibit common visuo-spatial deficits allow more specific conclusions to be drawn as to the underlying neural substrates of visual attention and spatial representation (see Heilman, Watson, & Valenstein, 1993; Leibovitch et al., 1998; Perenin, 1997; Robertson, Lamb, & Knight, 1988). With regard to unilateral neglect, which can arise from quite extensive lesions in some cases and quite focal lesions in other cases (see Driver & Vuilleumier, 2001, for an excellent review), this can be a particularly useful technique for articulating the neuroanatomy of visual attention and spatial representation. This approach has been particularly successful in determining the specific neural correlates of speech coordination in brain-damaged patients exhibiting language deficits (Dronkers, 1996).

In comparing the sensitivity of standard assessments of neglect with those of computerized RT measures, we direct the reader to a recent study by Deouell, Sacher, and Soroker (submitted). Deouell et al. have recently developed and administered a dynamic assessment of spatial attention to a large group (N=48) of right and left hemisphere damaged patients (Deouell et al., submitted; Deouell et al., 2000). By presenting targets in varying positions among a background of dynamically changing (“twinkling”) distractors, their “Starry Night” test assesses the distribution of attention over a computer screen while eye fixation is monitored via video camera. The combined collection of both accuracy (number of hits) and reaction time data allow for an evaluation of speed-accuracy tradeoffs in addition to statistical comparisons between target detection in the right and left visual fields. Evidence for a speed-accuracy tradeoff (faster RTs and more errors) would indicate a criterion shift or some difference in strategy for responding to left-versus right-sided targets. Deouell et al. found no evidence of a speed-accuracy tradeoff (faster RTs were accompanied by fewer errors). Thus, differences in RT could be attributed to differences in perception across the two visual fields. Patients with neglect should be slower and less accurate on the neglected side, and they were. Importantly, Deouell et al. also compared patients’ performance on the “Starry Night” task with that of the Behavioral Inattention Test (BIT), a standardized battery of attention tests (Wilson, Cockburn, & Halligan, 1987). Of the 12 right hemisphere damaged patients who performed within the “normal” range on the BIT, 6 (50%) demonstrated significant visual field differences in the Starry Night task. Another patient, who had initially scored abnormally on the BIT, continued to demonstrate a significant visual field difference on the Starry Night task despite the fact that his BIT score recovered to within normal limits at 14 weeks poststroke. These findings emphasize the increased sensitivity offered by RT measures.
Another nice quality of using computers and RT measures is that in addition to revealing any biases in the distribution of attention, each patient’s data can be swiftly converted into a pictorial representation of his/her attentional gradient (Fig. 2). This can also be helpful in distinguishing symptoms of neglect from those of a visual field cut because field cuts are typically delineated by sharp borders between normal and affected regions whereas neglect often manifests as a gradient with performance becoming progressively worse as targets are presented further into the contralesional side of space (Kinsbourne, 1987; Ladavas, Petronio, & Umlita, 1990). Thus, RT measures can also be useful clinically.

We now turn to some specific examples of how RT studies in neglect patients have contributed to our understanding of the neglect syndrome and the neural structures involved in human visual attention and spatial representation. As alluded to above, it is clinically and experimentally of interest whether neglected items suffer from a degraded representation of the contralesional side of space, or alternatively, from an abnormal attraction of attention to ipsilesional stimuli. The latter is consistent with studies providing evidence of graded performance across the visual field, but an understanding of exactly how, or by what, attention is captured following brain damage is essential to both rehabilitation efforts and our understanding of the neurology of attention. A study conducted by Grabowecky, Robertson, and Treisman in 1993 strongly suggests that the center of mass of a stimulus array spread over the visual field may influence the distribution of attention in neglect patients.
These investigators used a visual search paradigm where patients with acute neglect were asked to search an array for a particular target. Importantly, the stimulus arrays were sometimes flanked by various arrangements of distractors and search times were compared across these conditions. Flankers located on the ipsilesional side of the array had the effect of shifting targets relatively further into the contralesional (neglected) side of the display and exacerbating detection impairments (Fig. 3). In contrast, contralesional flankers shifted targets relatively further into the ipsilesional (intact) side of the display and often improved detection. Note that the placement of the flankers caused shifts in the relative positions of the targets, but not their absolute locations. This suggests that stimulus factors which influence an object’s perceived center of mass help determine the degree to which attention is unevenly distributed within a display following unilateral brain damage. This study nicely demonstrates how RT studies can examine how various stimulus factors may contribute to pathological attentional biases.

Another study employing a similar visual search paradigm was conducted in patients with focal brain lesions, 1 year poststroke (Eglin, Robertson, & Knight, 1991). In this study three different groups were formed on the basis of lesion location including patients with dorsolateral prefrontal cortex lesions, lateral parietal and temporal-parietal lesions. Both this study and an earlier study (Eglin, Robertson, & Knight, 1989) confirmed that delays in search times for contralesional targets increased linearly with increasing numbers of distractors presented in the ipsilesional side of space (at least this was the case when a serial search strategy was necessary, e.g., when searching for a feature conjunction among distractors that contain one or the other relevant feature but not both). These data are in agreement with others showing that greater attentional demands elicit greater search asymmetries in patients with unilateral brain lesions (Mark, Kooistra, & Heilman, 1988; Posner et al., 1984). Interestingly, the severity of the contralesional deficit did not differ significantly across the three patient groups in this study (although mean
search rate appeared somewhat slower in the temporal-parietal group. Thus, frontal, temporal, and parietal structures are all likely to be part of a neural network for directed attention.

Other studies have associated different anatomical regions with different components of the neglect syndrome implicating the parietal lobes in disengaging attention from previously attended stimuli, midbrain structures for moving attention, and the thalamus for engaging attention (see Rafal et al., 1988). One caveat that should be heeded when attempting to correlate behavioral deficits with specific neuroanatomical regions is that patients tested relatively soon after cerebral insult will almost certainly be suffering from edema and more widespread chemical and electrical effects from the initial insult. Thus, brain-behavior correlations are best interpreted when a sufficient amount of time (approximately 6 months to a year) has passed since the initial trauma. The downside, of course, is that the florid symptoms of neglect have often disappeared by then and substantial reorganization and compensation may have occurred. As with everything in life, there are always cost-benefit tradeoffs to consider when designing studies to answer these kinds of questions.

Another noteworthy aspect of Eglis et al.’s (1991) results is that contralesional deficits were not more often associated with right hemisphere damage than left. Search rates were the same and an attentional bias to start search on the most ipsilesional side was prevalent with both left and right hemisphere damage. Since this study was very sensitive to delayed processing of contralesional items, it is possible that more sensitive test measures will reveal that subtle impairments in contralesional stimulus processing occur more frequently with left hemisphere damage than previously thought. Furthermore, it is also possible that many traditional tests of neglect which contain multiple local elements to be searched, copied, or canceled are more sensitive to an abnormal capture of attention to local elements on the contralesional side of the display (Robertson & Rafal, 2000). Since right hemisphere lesions typically result in a bias to attend to local elements rather than the configuration as a whole, neglect may be magnified in right hemisphere patients, particularly when conventional assessments, or displays with multiple local elements, are used.

In addition to investigating how external stimulus factors influence neglect, RT measures can also be used to reveal the level of internal spatial representation that is affected. Since neglect patients exhibit marked differences in their perceptual/behavioral responses to stimuli in one side of space versus the other, they provide a special case in which the spatial representations that are being accessed/attended can be investigated. For instance, when sitting upright with an object placed centrally, the patient may neglect the object’s left side, which of course would also fall to the left of the subject’s body. However, when either the object or the subject’s body is rotated 90°, viewer-centered, object-centered, and/or environment-based reference frames can be decoupled. For example, Calvanno, Petrone, and Levine (1987) asked patients with left-sided neglect to identify targets while sitting upright, or lying on their left (or right) side. When subjects were seated upright, they named fewer items on the left side of the display as would be expected. When the subjects were lying on their sides, they named fewer items on their personal body-centered left as well as on the left side of the environmentally defined midline. Other investigators have observed similar results by tilting subject’s heads (Ladavas, 1987) and rotating common objects with respect to the viewer (Farah, Brunn, Wong, Wallace, & Carpenter, 1990).

A particularly revealing study by Behrmann and Tipper (1999) reported findings from a group of patients showing neglect in various spatial reference frames. Using a simple target detection paradigm while measuring RT, Behrmann and Tipper (1999) demonstrated that attentional orienting could be dissociated for viewer- and object-centered reference frames. The displays in their task contained two static boxes, and two differently colored circles that were connected with a bar to form a barbell (Fig. 4).

After the initial display was previewed (almost 3 s), a target could appear with equal likelihood in either of the two boxes or in either end of the barbell. On static trials, the target appeared some-
where within the initially presented display. On dynamic trials, the barbell dynamically rotated, such that the end that was originally in the patients' neglected field moved into the “good” field and vice versa and then the target appeared. In either case, the two boxes remained stationary. As expected, viewer-centered neglect was obtained for targets appearing in static (nonmoving) objects. Within the rotating barbell, however, detection was impaired for the end that had initially been presented in the neglected side of space, despite its having rotated into the “good” field prior to target presentation. But the most striking result was that even when the rotated object shifted neglect, keeping it with the object-centered frame, performance remained the same for targets appearing in the stationary boxes. In other words, target detection within the rotating stimulus revealed neglect within an object-centered reference frame while target detection in the boxes revealed a viewer-based impairment whether or not the barbell had rotated. The parsimonious explanation is that the cooccurrence of both viewer-centered and object-centered neglect in these patients likely reflects damage to a spatial attention mechanism that accesses information represented in multiple spatial reference frames.

Although the manifestation of neglect within multiple reference frames is of great interest to research on spatial representation in the brain, it is also of clinical relevance. To the extent that neglect is present in any nonretinotopic reference frame, it can be concluded that there is a visuo-spatial impairment beyond that of a primary visual field defect. Finally, the degree to which neglect is observed in more than one reference frame in a given patient may provide a means of quantifying the pervasiveness of visuo-spatial deficits in a manner than may turn out to be of neuroanatomical relevance. Current neurophysiological data in monkeys support the notion that the parietal lobes play an integral role in transforming retinotopic inputs into various coordinate representations (see Andersen, Snyder, Li, & Stricanne, 1993 for an overview), and evidence for object-centered and body-centered spatial representations have been obtained from neuronal recordings in frontal cortical regions (Graziano & Gross, 1998; Olson & Gettner, 1995).

In summary, there are numerous reaction time studies that have contributed to our current understanding of the syndromes of unilateral neglect and extinction as well as our understanding of the neural basis of visual attention and spatial representation. Here, we have simply highlighted a few selected studies that illustrate some of the advantages of reaction time measures that are often both clinically and experimentally relevant. We hope to have illustrated here how the bridging of clinical neuropsychology and cognitive neuroscience can produce bi-directional benefits to both fields, as well as potentially improve patient care.

Fig. 4. Target detection task used by Behrmann and Tipper (1999). Numbers in the rightmost panel reflect eight patients’ mean and median RTs to detect targets in various positions after rotation of the barbell. Within the stationary squares, patients were slower to detect left-sided targets. Yet within the rotated barbell, they were slower to detect targets on the right side of the display (i.e., the leftmost circle prior to rotation).
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