

Shifting Spatial Neglect With Repeated Line Bisections: Possible Role of Lateralized Attentional Fatigue

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Background and Objective: Many patients who have signs of neglect immediately after a right hemisphere stroke remain disabled even when they improve on tests of neglect. Few patients are tested for attentional persistence and fatigue despite their importance in many instrumental activities. To investigate whether stimulus repetition might alter the allocation of attention, we repeatedly tested a patient 16 weeks after she developed hemispatial neglect from a right hemisphere stroke.

Methods: During each of three testing sessions given in 1 day, we asked the patient to bisect 90 lines of two lengths, presented in 30-trial blocks in three locations: left, center, and right of her midsagittal plane, partially counterbalanced across sessions. We adjusted multiple regression analyses and analysis of variance as well as post hoc regression and *t* tests for persistence in the repeated measures using variance-sample size analysis to estimate self-similarity, a measure related to the fractal correlation dimension.

Results: In each session, the patient's line bisections revealed transient leftward bias in her left peripersonal space, and constant rightward bias in her right peripersonal space. Her leftward bias shifted to a rightward bias over repeated trials in her left space.

Conclusions: The patient's left-to-right shift with repeated trials suggests either fatigue from an attempted compensation for leftward inattention or habituation of a contralesional spatial attentional attraction, revealing contralesional left-sided neglect in both the left and right spaces. Future studies are needed to learn if other patients show similar or different deficits with repetition, and how best to treat them.

Key Words: ipsilesional spatial neglect, contralesional spatial neglect, inattention, hemianopia, habituation

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ANOVA = analysis of variance. IID = independent and identically distributed. NS = not significant.

Patients with right hemisphere injury are more likely to be disabled than patients with left hemisphere injury, and spatial neglect increases the likelihood of disability (Katz et al, 1999). Because in most patients the signs of contralesional spatial neglect abate over weeks to months (Suzuki et al, 1997), the source of this disability is not entirely understood. Although spatial processing does change over time, one of the reasons why patients who remain disabled appear to have recovered from their spatial neglect is that clinicians may not be testing them thoroughly.

Three of the most common methods for assessing unilateral neglect are bisecting lines, identifying spatially distributed symbols in the context of distractors (the cancellation test), and spontaneously drawing or copying pictures. The choice of testing method can alter the clinician's ability to detect and assess the severity of neglect (Heilman et al, 2012).

When patients perform the line bisection task, the portion of the line to which they attend appears longer than the objectively equal portion of the line to which they are not attending. Patients who are inattentive to one side of space will, therefore, deviate their bisection toward the part of the line to which they are attending (Heilman et al, 2012).

Not only can the line's attributes alter the results, but so can the way the line is presented. For example, bias is often more severe when the line is placed in the contralesional than the ipsilesional hemispace (Heilman and Valenstein, 1979). Longer lines are more likely to show spatial bias (Nicholls et al, 2016). The farther away the line is from the participant, the less the spatial bias (Nicholls et al, 2016). If the line is made up of characters or letters, rather than being a solid rule, the participant's bisection may deviate more to the right because the characters or letters activate the left hemisphere (Lee et al, 2004).

Although many studies have examined how different conditions can influence the bias in patients with hemispatial neglect, little is known about the influence of repeated testing.

Some basic and instrumental activities of daily living must be executed repeatedly or be maintained over a period of time to be completed successfully. People may

become progressively less attentive to stimuli that have been presented repeatedly or to stimuli to which they have been exposed for a long period of time. Because patients with neglect already have an impairment of their attentional-arousal networks (Heilman, 1979; Heilman and Valenstein, 1979), these people may show abnormally early attentional fatigue, even with meaningful repeated stimuli. This abnormal attentional fatigue, like attentional neglect, may be more severe in patients' contralesional than their ipsilesional hemispace. Such a deficit may help explain these patients' chronic disability.

The goal of our study was to test this attentional fatigue hypothesis in a patient who had evidence of contralesional hemispatial attentional neglect.

CASE REPORT

A 48-year-old right-handed woman was admitted to the hospital with sudden-onset severe right retro-orbital pain and left-sided weakness.

Until this admission, the patient had been a practicing registered nurse who ran an inpatient facility. Her extensive medical history included a non-ischemic cardiomyopathy, congenital heart block (managed with a pacemaker), mitral valve prolapse, sequential right and left renal infarcts, intermittent depression, hyperlipidemia, hypothyroidism, Sjögren syndrome, and a suspected small cerebral infarction that had caused a transient right superior quadrantanopia.

On this admission, neurologic examination revealed left-sided neglect, a left homonymous hemianopia, difficulty with leftward lateral gaze, and a left hemiparesis with lower facial weakness. Thin-section computed tomography revealed a large right hemisphere infarction in the distribution of both the middle and posterior cerebral arteries. There was a 3-mm midline shift to the left, but no hemorrhagic transformation. The right middle cerebral artery appeared to contain a thrombus.

The day after admission, a repeated computed tomogram revealed a 9-mm midline shift to the left, and uncal herniation. The patient underwent a craniotomy with decompression. Postoperatively she suffered respiratory failure, requiring a tracheostomy and mechanical ventilation. She was eventually discharged home, but could not walk and needed 24-hour care.

On a follow-up evaluation 16 weeks after her stroke, she was alert, still with left hemiparesis. She felt light unilateral touch on the left or right side of her body, but when touched on both sides at once, she did not detect the left-sided stimuli.

She appeared to have a rightward spatial attentional bias. On the line bisection task, when the line was presented directly in front of her so that her midsagittal plane bisected the line, she marked the line 4.7 cm to the right of midline (21% deviation). On the line cancellation test, she failed to cancel 21 of 40 lines; 20 of those 21 lines were on the left side of the page. When we asked her to copy a daisy, a house, a cube, and a clock, her drawings had gross distortions of design elements and many omissions of left-sided features.

She was aware of her left hemianopia and had learned to turn her head and body to see the left side of her environment. Her visual pursuit was smooth to the right and saccadic to the left. Her distance-corrected visual acuity was 20/30 in each eye.

We could not test her gait and balance because she was confined to a wheelchair.

Because her spatial judgments differed so strikingly depending on which side of her peripersonal space we presented line bisection stimuli, we wanted to learn reliable characteristics of her neglect. She agreed to let us give her extended line bisection testing.

Line Bisection Task

The stimuli were black horizontal lines either 200 mm or 240 mm long, printed on white sheets of 280-mm-wide paper. The examiner presented these sheets to the patient one by one and asked her to mark the middle of each line using her right (non-paretic) hand.

The testing was conducted on 1 day in three consecutive sessions. Each session had 90 trials divided into three blocks of 30 trials. The patient was given a 1-minute rest period after each 30-trial block and a 5-minute rest period after each 90-trial session. Each 30-trial block had 15 trials with the 200-mm lines and 15 trials with the 240-mm lines. The examiner presented the different line lengths in quasi-random order, with at most four consecutive trials of the same length. The patient performed each block of trials with the paper in one of three possible locations in her peripersonal space:

- Center space: stimulus midpoint at her midline
- Left space: stimulus midpoint 140 mm to the left of her midline
- Right space: stimulus midpoint 140 mm to the right of her midline

Over the three testing sessions, we partially counter-balanced for block order.

The patient's deviations from the objective midpoint of the line were measured to the closest millimeter. Because we used lines of two different lengths, each deviation was converted to percent deviation relative to the line length.

We lost seven trials because of ambiguous marks or experimenter errors. The errors were spread nearly uniformly across session or block orders, locations, and line lengths, but it is notable that six of the seven errors occurred during the latter trials within a block.

Data Analysis

The modest number of observations that we obtained was insufficient to power a full factorial analysis of variance (ANOVA). Full factorial ANOVA would have included all five variables in one calculation, resulting in too few observations per cell because of the larger total number of cells, and thus risking failure to detect systematic effects and interactions (assuming $P < 0.05$). Because our hypothesized "hemispatial attentional fatigue" mechanism implies systemic interactions, we instead used multiple regression

for first-order analyses. First-order analyses test for effects of the three variables of neurologic relevance (line length, location, and trial order) by temporarily excluding two less important variables, block order and session order.

The first-order analyses enabled second-order analyses on the first-order residuals to test for effects of the two previously ignored variables (block order and session order) and for main effects without considering trends. In essence, second-order analysis of the residuals treats the first-order relevant variables as if they were variables of no interest.

Finally, we used post hoc simple regressions to further characterize linear trends evidenced by multiple regressions. We used post hoc nonparametric binomial tests to look further for trends. In all of these analyses, we interpreted statistical outcomes using persistence-corrected degrees of freedom, as described in the rest of this section.

Analyzing data from a single patient poses two special challenges. First, inferences to the general population are tenuous by definition (Laws et al, 2005). Second, inferential statistics typically require independent observations as replicates to specify the degrees of freedom associated with the sampling distribution of the statistic. It is not valid to assume independence of repeated observations made on the same individual.

To check our series of repeated observations for interdependencies, we used ordinary least-squares (Pearson) autocorrelation, both on successive judgments regardless of line length and on successive judgments given the same line length. We also used estimates of self-similarity, a measure in nonlinear dynamic systems analysis. Self-similarity, related to the fractal correlation dimension and to deterministic chaos (Gao et al, 2007), has been applied medically, eg, to classify brain activation in functional magnetic resonance imaging (Lee et al, 2008), but not previously, to our knowledge, for neuropsychological data. As further detailed in the next paragraphs, self-similarity can let us estimate the loss of degrees of freedom associated with the sampling distributions relied on to interpret ANOVA or regression statistics.

Variance-sample size analysis to estimate self-similarity relies on the principle that variances of means (the squares of estimated standard errors of the means) are inversely proportional to the number of independent replicate observations used to calculate the means. This same principle is critical to interpreting ANOVA or regression outcomes. Inverse proportionality between the variances of means, and the sample sizes used to calculate the means, requires strict averaging of independent and identically distributed (IID) samples so that each sample creates a degree of freedom. We divided our empirical series of observations into non-overlapping subsamples of different sizes, means obtained for each subsample, and variances calculated for all the means of each subsample size.

An index of self-similarity, the Hurst exponent, can be estimated from the best-fitting power function relating these empirical variances of means to the subsample sizes used for calculating the means. When this power is -1 , then inverse proportionality between these quantities is

supported, consistent with the observed data comprising the IID samples. When this power lies between -1 and zero, the quantities are described as having persistent self-similarity (the second moment is “too smooth”). When this power is < -1 , the quantities are said to have anti-persistent self-similarity (the second moment is “too rough”).

Self-similarity can detect nonlinear and/or long-range correlations to which Pearson autocorrelations are insensitive. Significant nonlinear or long-range correlations give evidence incompatible with IID samples. Because the sampling distributions of self-similarity indices are typically unknown, interpretation relies on bootstrapping from the observed time series. Randomly shuffling the observations destroys mutual information based on temporal sequence without changing any distributional characteristics.

In our study of this patient, we randomly shuffled each block series eight times. If at least seven of the eight shuffled surrogate series exhibited power closer to -1 than the unshuffled series, then the unshuffled observations seemed unlikely to be as temporally independent as the randomly shuffled ones ($P < 0.05$, binomial test).

We adjusted effective degrees of freedom for second moment statistics to account for persistent self-similarity by raising to the empirically estimated powers, and then rounding to whole numbers the applicable degrees of freedom if we had instead observed IID samples. Using thus-reduced effective degrees of freedom lessens the likelihood of falsely rejecting the null hypothesis by making the second moment statistics “rougher.” The described calculation might overly reduce effective degrees of freedom for nonstationary time series (Hu et al, 2004) such as those that we had observed in our patient’s left peripersonal space.

RESULTS

We found positive Pearson autocorrelations between immediately successive (without regard to line length) bisection judgments in the patient’s right space ($r^2 = 0.14$, $F_{1,34} = 5.91$, $P < 0.03$) and center space ($r^2 = 0.24$, $F_{1,23} = 7.63$, $P < 0.02$), but not her left space ($r^2 = 0.15$, $F_{1,18} = 3.52$, not significant [NS]). Autocorrelations were not significant past immediately neighboring successive judgments or between successive judgments of only the same line length, in any location. Comparisons against randomized surrogate data showed significant ($P < 0.05$, binomial tests described above in *Data Analysis*) sequential persistence in left (power = 0.66) and center (power = 0.71) but not right (power = 0.80) space.

Figure 1 compares deviations (% of line length) of bisection judgments from the objective midpoint of the line, as a function of trial order within a 30-trial testing block.

In the following results, a minus sign preceding a percent deviation denotes leftward deviation, not negative distance.

For bisections judged on 200-mm lines, multiple regression of successive trials made in the three spaces revealed no statistically significant linear trends:

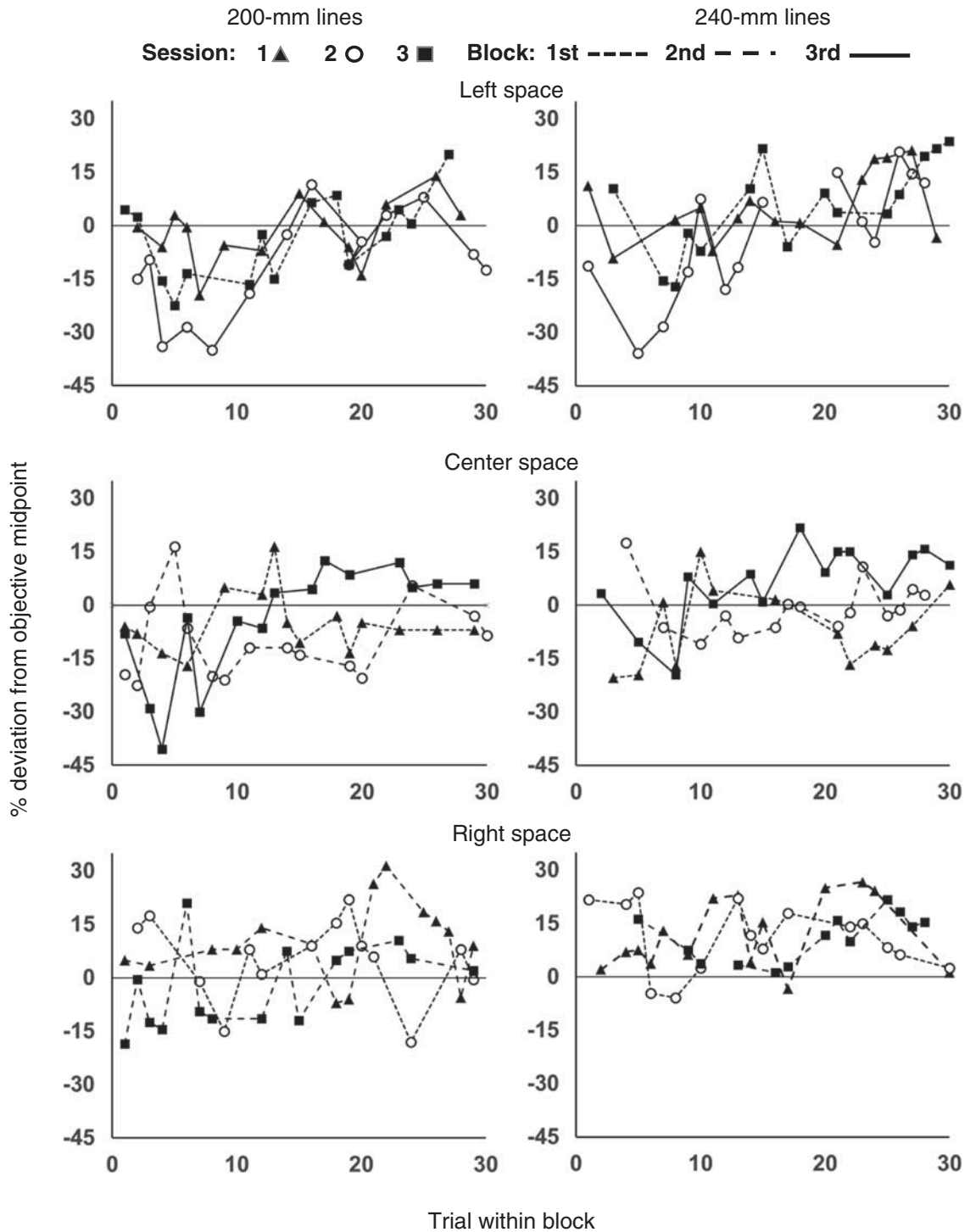


FIGURE 1. Percentage deviation of this patient’s bisection judgments from the objective midpoint, as a function of trial order within a 30-trial testing block. The objective midpoint is shown as a horizontal grid line at zero in each panel’s Y-axis. The panels on the left side of the figure show results obtained with 200-mm lines; the right panels, results with 240-mm lines. The top panels show results obtained in the patient’s left peripersonal space; the center panels, results from her center space; and the bottom panels, results from her right space. Symbol shapes denote session: Session 1 = triangle; Session 2 = circle; Session 3 = square. Connecting lines denote the order of the three blocks within the session: 1st = dotted lines; 2nd = dashed lines; 3rd = solid lines. Because the examiner inadvertently swapped the planned sequence of two conditions, the two top graphs show two solid connecting lines and no dashed line, and the two bottom graphs show two dashed connecting lines and no solid line.

TABLE 1. Selected Statistics from Post Hoc Regression Analyses of Our Patient's Line Bisections: Percent Deviation as a Function of Trial Order

Judgment Condition		Regression Statistics					
Peripersonal Space	Line Length (mm)	Slope*	Standard Error of the Slope†	<i>t</i>	Degrees of Freedom†	<i>P</i> ‡	<i>r</i> ² §
Left	240	1.93	0.76	2.54	11	0.01	0.36
	200	1.17	0.79	1.49	11	0.08	0.15
Center	240	0.82	0.67	1.23	13	0.12	0.08
	200	0.96	0.72	1.33	14	0.10	0.09
Right	240	0.35	0.47	0.74	19	0.23	0.01
	200	0.43	0.64	0.67	19	0.26	< 0.01

*Rate of change of % deviation from objective midpoint per trial.

†Adjusted for persistence.

‡Likelihood for a value of the *t* statistic \geq that observed given the applicable degrees of freedom.

§Goodness of fit of a linear regression model for the corresponding conditions.

$r^2 = 0.22$, $F_{3,15} = 1.01$. Lack of trends over trials supports using one-way repeated measures ANOVA to examine the main effect of location: $F_{2,45} = 3.88$, $P < 0.03$.

On post hoc analyses, these deviations on 200-mm lines mostly showed significant leftward bias: grand mean -3.4% , $t_{44} = -1.69$, $P < 0.05$; left space mean -5.4% , $t_{22} = -2.08$, $P < 0.03$; and center space mean -6.6% , $t_{28} = -2.84$, $P < 0.01$. In right space, however, the deviations showed rightward bias: mean 4.3% , $t_{44} = 2.36$, $P < 0.02$. Post hoc two-way ANOVA using residuals on 200-mm lines did not find main effects for session order ($F_{2,34} = 0.74$, NS), block order ($F_{2,34} = 0.55$, NS), or session order \times block order interactions ($F_{4,34} = 0.84$, NS). These results indicate no consistent evidence of an overall learning effect.

For bisections on 240-mm lines, multiple regression revealed marginally significant interactions of successive trials made in the three spaces: $r^2 = 0.37$, $F_{3,15} = 2.99$, $P = 0.06$. In post hoc analyses, deviations on the 240-mm lines showed significant rightward bias (grand mean 3.8% , $t_{44} = 2.09$, $P < 0.03$; right space mean 11.25% , $t_{32} = 7.34$, $P < 0.01$) or no significant difference from objective bisection (left space mean 2.65% , $t_{22} = 0.91$, NS; center space mean 0.03% , $t_{28} = 0.01$, NS).

Post hoc two-way ANOVA using residuals on 240-mm lines did not find main effects for session order ($F_{2,37} = 0.87$, NS), block order ($F_{2,37} = 0.13$, NS), or session order \times block order interactions ($F_{4,37} = 1.18$, NS). Again, there was no consistent evidence of an overall learning effect.

The post hoc regression analysis illustrated in Figure 1 showed a significant linear trend over successive trials in left space for bisections on 240-mm lines: $F_{1,11} = 6.60$, $P < 0.03$ (Figure 1, top right panel). For the other conditions, regression analyses showed a linear trend over trials (left space, 200-mm lines, top left panel), weak linear trends over trials (center space, 200-mm and 240-mm lines, center panels), or no evidence of linear trends over trials (right space, 200-mm and 240-mm lines, bottom panels).

Table 1 shows selected statistics from these regression analyses. Across the two line lengths: In the first 10 trials of the three left space trial blocks, 22 of 30

deviations from the objective midpoint were leftward; in the last 10 trials of the three left space trial blocks, 23 of 30 deviations were rightward. These proportions would be unlikely to occur by chance if leftward and rightward deviations were equally likely ($P < 0.01$, binomial tests adjusted for persistent self-similarity).

DISCUSSION

The lack of statistical independence in one patient's repeated judgments makes it difficult to identify reliable effects. We adjusted our inferential statistics for the persistent self-similarity that we observed in the repeated measures. This adjustment reduced the likelihood of falsely rejecting the null hypothesis. This adjustment also reduced the likelihood of correctly detecting systematic linear trends because the persistence adjustment can be mis-estimated when there is true covariance (Hu et al, 2004). This is most easily seen in Table 1 by the persistence-adjusted degrees of freedom increasing progressively, despite the similar number of observations made per condition.

By contrast, the goodness of fit (r^2) of a linear regression model for the corresponding conditions has values that decrease progressively down Table 1. In other words, persistence adjustment sacrifices degrees of freedom roughly in proportion to the strengths of the linear trends. If the persistence adjustment power described above had been mis-estimated by as little as 10% of its value, then the results obtained in left space with 200-mm lines would also have been found to be significantly trending over trial blocks. The persistence adjustment calculations affect standard errors and *t* statistics as well as degrees of freedom, so that influences on statistical significance cannot be easily extrapolated from Table 1.

Healthy participants may deviate to the left on line bisections when the line is directly in front of them ("pseudoneglect" in center space), and healthy participants do not deviate consistently from objective bisection when the line is placed in their right space (Jewell and McCourt,

2000). In contrast to healthy participants, our patient did not have significant bias when the line was in front of her, and her bisections on both line lengths showed a significant rightward bias in her right space.

For many patients who have neglect from a right hemisphere infarction, line bisection shows greater rightward deviations in left than in right space (Heilman and Valenstein, 1979), suggesting that bias is primarily being mediated by hemispacial inattention. Our patient did not show that common pattern. It is noteworthy that we assessed her almost 4 months after her stroke, whereas Heilman and Valenstein (1979) studied patients with acute strokes. When tested with 200-mm lines, except as just noted for right space, our patient showed slight leftward biases. When tested with 240-mm lines in left space, she initially showed a strong leftward bias.

We are not aware of previous line bisection studies that showed rightward deviation in right hemispace (contralesional neglect) apparently coexisting with leftward deviation in left hemispace (ipsilesional neglect). This apparent coexistence is transiently revealed in the beginning of our patient's left space trial blocks.

Furthermore, her left and right hemispaces reacted differently to repeated stimulus presentations. In right space her rightward bias was consistent over repetitions, but after many repeated trials in left space she developed a rightward instead of a leftward bias. Repeated trials appeared to affect her performance in her left space more than her performance in her center or right space during the same testing session.

Unlike generalized fatigue, which might build over all the trials in a session, her effect seemed to grow convincingly during the blocks of trials in left space but not during the center or right blocks of trials during the same sessions. Future studies should test this suspected spatial specificity more rigorously by varying how trials in the three spaces are interleaved.

These findings are consistent with the postulate that abnormal attentional fatigue may be more severe in the contralesional than ipsilesional hemispace. However, mechanisms underlying these findings are not entirely known. Prior studies have suggested that some patients who initially show contralesional neglect can, over weeks to months, develop a bias that is instead consistent with ipsilesional neglect (Drago et al, 2006; Kwon and Heilman, 1991). This later-developing bias has been posited to be induced by a contralesional hyperattention (attentional attraction) rather than by ipsilesional inattentional neglect (Kwon and Heilman, 1991). However, it is also possible that the changing line bisection biases are related to a patient's learned compensatory strategy (Barrett et al, 2003), and further studies should examine these alternative hypotheses.

According to a model of attentional attraction ("grasp"), our patient's right (lesioned) hemisphere's ability to sustain an attentional grasp diminished over repeated trials and recovered between sessions. At the same time, the left-sided allocentric spatial inattention induced by her right hemisphere injury, or by her disinhibited left (intact) hemisphere's enhanced contralateral hyperattention

(Kinsbourne, 1970), was unaffected by the repetition (Finney et al, 2015).

She first showed leftward bisection deviations in her left space, consistent with a contralesional hyperattentional grasp. Placing the stimuli in her left space may have enhanced her right-hemisphere-mediated leftward attentional grasp, while placing the stimuli in her right space may have reduced her right-hemisphere-mediated leftward grasp. In addition, her right hemisphere lesion could have disinhibited her left hemisphere attentional networks, and placing the stimuli in her right space may have activated these networks, thereby promoting rightward hyperattention in her right hemispace.

We can also consider the possibility that the patient learned to compensate to some extent for her leftward inattention. If this model is true, it is noteworthy that she had a left field hemianopia and, unlike most patients with neglect from a parietal lesion, who are unaware of their visual field deficit (Warrington, 1962), she was aware of hers. Patients with hemianopia have been shown to bisect lines toward their hemianopic field, and this error has been posited to be related to attempted compensation (Barton and Black, 1998).

Our patient's initially leftward deviation in left space (possibly related to her attempt to compensate for her hemianopia) may have been effortful, and perhaps she could not fully sustain the effort over the repeated trials during a testing session. The declining leftward bias seen first in her left space thus gradually changed to a rightward bias (contralesional neglect). Recovery between sessions would presumably have allowed her refreshed compensatory system to start again allocating attention to left space. The deviation would begin leftward, but would gradually become more rightward, revealing her right-hemisphere-mediated contralesional neglect in left space across the repeated trials. The contralesional neglect in her left space would match the contralesional neglect continuously evidenced in her right space.

The model of attentional grasp described earlier and a model of learned compensation here briefly described seem equally capable of explaining our patient's performance.

Kwon and Heilman (1991) gave line bisection tasks to a man with a right frontal cerebral infarction. On day 1, he showed left-sided (contralesional) neglect (rightward bias) that increased with repeated trials. When tested again on day 5, his bias had reversed and he showed right-sided (ipsilesional) neglect (leftward bias) that also increased with repeated trials. By contrast, our patient's directional bias first decreased with repeated trials, but then it increased in the opposite direction. Because her pattern with repeated trials differed from that of the earlier patient, the mechanism that induced her judgment biases may differ from the mechanism that induced his ipsilesional neglect (Kwon and Heilman, 1991). The reason for this difference is not known.

Our purpose in this study was to test a patient who had contralesional hemispacial attentional neglect to learn if abnormal attentional fatigue, like attentional neglect, may be more severe in contralesional than ipsilesional hemispace. Our patient did show hemispatially asymmetric attentional fatigue, as hypothesized. Unfortunately, the repetitive line bisection

testing required for this study was so long and intensive that we did not have time available to test many of her other cognitive functions. Further neurobehavioral testing might have helped explain the brain mechanisms responsible for her performance with repeated testing. Future studies are needed to explain these mechanisms as well as differences between patients who do and do not show this pattern of behavior. Because abnormal attentional fatigue could be a source of chronic disability, more research is needed to learn the best means to treat and manage the condition.

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