Is motor perseveration in unilateral neglect ‘driven’ by the presence of neglected left-sided stimuli?

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Abstract

Unilateral spatial neglect refers to a difficulty in detecting or acting on information in a particular region of space. When asked to cross out stimuli distributed across a page, patients with neglect may miss many targets on the left. In addition, they have a tendency to return to, and re-mark, right-sided targets that they have already cancelled. A recent retrospective study has shown this effect to be specific to unilateral neglect rather than a consequence of right hemisphere damage in general. Here, a consecutive group of seven right-hemisphere neglect patients performed five versions of a standard cancellation task, each version differing in the quantity of left-sided information presented. All of the participants showed perseveration on right-sided targets in the basic task. A highly significant and linear reduction in perseverative behaviour was observed as left-sided information was removed. In a second study, left-sided targets were again progressively removed but, in this case, were replaced with an additional distracter item, keeping the total quantity of stimuli presented in each condition constant. Again, a significant reduction in right-sided perseveration was observed, indicating a high degree of selectivity to the effect. The results show that a difficulty in perceiving existing cancellation marks, or a non-spatially specific motoric perseveration, are unlikely to fully account for this behaviour. As the patients omitted almost all targets on the left side of the basic cancellation task, the results suggest a striking influence on apparently intentional behaviour from un-cancelled information within the neglected field. © 2002 Elsevier Science Ltd. All rights reserved.

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1. Introduction

Perseveration refers to the continuation or recurrence of a behaviour or experience that is in some way contrary to an individual’s current goal, or which persists in the absence of an appropriate external stimulus [20,30]. Although, given this broad definition, perseveration can be seen as a relatively common feature of many normal human mistakes [27], a heightened vulnerability to such errors has long been reported in neurological patients. The variety of conditions associated with perseveration (e.g. dementia [16], frontal lesion [5,20,24], Huntington’s disease [19], and the variety of manifestations (e.g. repeating words, motor actions, getting stuck in a particular cognitive set) has led to debate about whether perseveration is best thought of as a relatively independent deficit or as a functional consequence of damage to other capacities [30].

Unilateral neglect refers to an acquired deficit in detecting, reporting, reaching towards, or—in some cases—even thinking about information from one side of space [2,4,28]. Although, forms of spatial neglect are observed following damage to either the right or the left hemisphere of the brain, chronic forms of the disorder are overwhelmingly associated with right hemisphere lesions [31,32].

In addition to a frank neglect of left space, neglect patients have been observed to exhibit behaviour that could be termed perseverative. Indeed, the clearest example lies in cancellation tasks, in which patients are asked to find and cross-out (cancel) visual stimuli distributed over a page. Here, patients may return to already cancelled targets and re-mark them—once or on repeated occasions—without any clear reason [22,29]. Patients have also been observed to return to, and apparently needlessly elaborate, right-sided details in copying, drawing or bisection tasks [3,7,11]. Clinically we have sometimes observed patients to return to recently searched right-sided surfaces in an apparently perseverative manner, looking for ‘missing’ objects that are actually to their left.

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and to make repetitive gestures to right-sided objects for which there is no apparent immediate use.

Na et al. [22] retrospectively analysed the line cancellation sheets of 60 neglect patients. Approximately 30% of the sample showed evidence of perseveration (as indicated by two separate lines through a target), this being predominantly at the extreme right of the sheet. The frequency of perseveration was inversely related to accuracy on the task, that is the greater the neglect shown by a patient the more they tended to perseverate. Although, patients with anterior damage formed the majority of the group, perseveration was also observed in some patients with ostensibly purely posterior lesions.

A limitation in Na et al. study was that, through only examining the performance of right hemisphere patients with neglect, the specificity of this form of perseveration to the disorder was not known. A recent study by Rusconi et al. [29], has directly addressed this issue. The cancellation performance of 181 patients was retrospectively analysed. The continuous sample included patients with left hemisphere damage, right hemisphere damage (with and without clear symptoms of neglect) and patients with dementia of the Alzheimer’s type. Of the 31 right hemisphere patients showing neglect, 29 (90%) showed at least one perseverative response (the average number of perseverations being 5.31 range 0–25 [29]). This contrasted with only seven of the 60 patients with right hemisphere damage and no neglect. Left hemisphere lesions were in general associated with a low frequency of perseveration, although in the small group who showed neglect for the right side of space (n = 4), three patients evidenced this behaviour at least once. For the right hemisphere neglect patients, as with Na et al. study, perseverations overwhelmingly occurred on the right side of the sheet, and a significant (though not exclusive) association between the presence of frontal and subcortical lesions and this behaviour was observed.

The evidence to date therefore, indicates that perseveration of this type is both relatively common (affecting between 30 and 90% of neglect patients to some degree), and appears specifically associated with the presence of neglect, rather than with right hemisphere damage per se.

A number of general accounts for this phenomenon can be proposed. It is possible that patients simply have difficulty in ‘seeing’ their original cancellation marks (or fear that the examiner will not see them when scoring the test). The marks made by patients will often be more feint than the printed stimuli on a sheet, and possibly vulnerable to limited visual attention in the ‘good’ field and competition from surrounding stimuli [10]. It is also known that neglect patients have a tendency to return to previously inspected targets when performing a purely visual search task, i.e. when there is no visual marker of the previous visit—a finding that was interpreted in terms of an impaired spatial working memory [14,34]. If existing cancellation lines are not sufficiently salient in marking already visited locations, patients may quite reasonably return to them without this behaviour being considered perseverative.

A second possibility is that patients with neglect are vulnerable to an additional deficit that leads to perseveration. Although, in Na et al. [22] study there was an association between the severity of neglect and the frequency of perseveration, the absence of any such correlation in Rusconi et al. [29] findings is consistent with the presence of two relatively independent, although co-occurring, disorders. In accounting for their results, Rusconi et al. suggest that damage to the frontal cortex (and related subcortical structures) lead to disinhibition of motor control and a consequent tendency to repeat actions. However, given the relatively low levels of perseverative behaviour in right hemisphere patients without neglect, they suggest that the addition of the spatial bias (perhaps in giving right space a ‘magnetic’ attractiveness for patients) is necessary for the pattern of behaviour to be observed.

Na et al. [22], given their finding of an association between neglect severity and ipsilesional perseveration, considered a number of suggestions in which the appearance of perseveration is more integral to the spatial bias of the neglect disorder. Aspects of neglect have been framed, for example, as a difficulty in disengaging from right-sided stimuli [17,26]. Na et al. argue that the addition of the cancellation lines to right-sided stimuli could act to increase their visual salience relative to those on the left. In this manner, their capacity to compete with left-sided targets may exert a stronger influence in capturing the patients’ attention and action—drawing their search back repeatedly to the right.

A possibility that has not so far been considered is that the patients perseverative behaviour on the right side of the sheet is not so much ‘drawn’ by ipsilesional stimuli as ‘driven by information within left, neglected space. As discussed, we have observed patients returning to search a recently examined location on their right, such as a dressing table, in an apparently perseverative manner looking for objects that are in fact located to their left. This may occur because patients remember having recently used the object and, therefore, assume that it is present somewhere. It may also be that patients are ‘detecting’ the object but are either confused about its location, unable to make the reach into left space to retrieve it, or, in some manner, transpose this experience to their right side. As this action cannot achieve its goal, it is vulnerable to repetition and apparent perseveration. By analogy, repeated cancellation of right-sided targets in a cancellation task may reflect behaviour that is elicited by—or at some level directed towards—left-sided targets.

We will consider the mechanisms whereby this might occur further in the discussion. Firstly, to establish whether it was the case, and to test some of the predictions made by other accounts, in a prospective study we modified a standard cancellation measure [31]. In the standard condition, 56 targets and 72 distracters are randomly distributed across the full extent of an A4 sheet. Over the four new conditions, both targets and distracters were progressively removed from the
left side of the sheet, first to show 40 targets, then 27, then 16 and, ultimately, only a narrow strip of 8 targets and distracters at the extreme right.

Our predictions were as follows:

1. As with previous reports using different cancellation tasks [22,29], patients with unilateral neglect would show perseverations on right-sided targets on the standard, full-page task.

2. If patients cancelled previously marked targets because they had difficulty in seeing the existing cancellation marks—or were concerned that the examiner may not be able to see them—this should not be significantly affected by the presence or absence of left-sided information, and little or no modulation in perseveration should be observed across conditions.2

3. If patients returned to previously marked targets due to a form of ‘motor perseveration’ that is, independent of perceptual or sensory input—again, no significant modulation should occur with the removal of information from the left of the sheet.

4. Na et al. [22] suggested that perseveration may occur because the existing cancellation marks add to the attentional salience of the right side of the sheet. The removal of information from the left side of the sheet, in that it greatly adds to the salience of the remaining information on the right, may then also lead to an increase in perseveration on the right.

5. If, as we have proposed, perseveration may be ‘driven’ by the presence of un-cancelled targets on the left—or a more general sense that the task is ‘incomplete’, removal of left-sided targets should lead to a progressive decline in perseverative responses on the right.

2. Experiment 1

2.1. Method

2.1.1. Participants

In-patients at the Addenbrooke’s Hospital Stroke Unit were approached for participation in this study if their performance on a standardised cancellation measure [33] was consistent with a unilateral neglect. The seven patients who gave informed consent were a consecutive sample (i.e. patients were not selected on the presence of perseverative behaviour). The group was of mean age 74.71 years (S.D. 5.92), 7.14 (S.D. 3.32) and 4.14 (S.D. 3.72) and 0.57 (S.D. 0.28).

2.1.2. Materials

The standard Star Cancellation test [33] consists of a white A4 (landscape orientation) sheet showing 56 black small star targets (8 mm × 8 mm) together with 72 black distracters (larger stars, letters and words) in a quasi-random distribution. Healthy individuals almost invariably detect all or the vast majority of the targets [33].

Four modifications were created by progressively removing both targets and distracters from the right side, the number of remaining targets in each condition being 40, 27, 16 and 8, respectively (see Fig. 1). These slightly uneven intervals in terms of target numbers were determined by the original layout of the task.

2.1.3. Procedure

All conditions were administered to patients in a single session in a random order. In each case, administration was identical and as for the standard measure, namely, with the centre of the sheet placed at the patients’ midline, the patients were asked to find and cross out as many as possible of the small star targets as possible. No restrictions were placed on eye or head movements and no time limit was imposed, the patients being asked to declare when the task was finished. No additional cues, for example, to continue or to stop were provided. To count as a perseverative patients had to return to a previously marked target (i.e. not simply draw two or more consecutive lines). Perseverations were recorded during performance using a counter kept out of sight.

2.2. Results

2.2.1. Perseverations

Perhaps somewhat surprisingly given Na et al. [22] results, all of the patients showed some perseverative responses on the standard version of the task, the greatest number being from FJ who returned to already cancelled targets on 24 occasions. As would be expected—and in line with the previous finding—these were predominantly made on the rightmost targets.

Fig. 2 shows how the number of perseverations declined as left sided information was removed from the materials. In the standard, full sheet condition, the patients made a mean of 16.28 perseverative responses (S.D. 7.73). With each subsequent removal of left-sided information this declined to 10.0 (S.D. 5.92), 7.14 (S.D. 3.29), 4.14 (S.D. 3.72) and 0.57 (S.D. 0.28).
(S.D. 0.79) perseverations, respectively. Repeated measures ANOVA with condition (1–5) as the levels of the factor, implemented in SPSS [23] confirms a statistically significant reduction ($F(1, 4) = 38.85, P < 0.001, \text{scores log10 transformed}$) that conformed to a linear trend ($F(1, 6) = 157.63, P < 0.001$). To examine this in more detail, $t$-tests were performed on each pair-wise comparison (condition 5 versus 4, 5 versus 3 and so forth) using Holm’s correction procedure for multiple post-hoc comparisons (see [13]). On this basis, all comparisons with the exception of adjacent conditions (1 versus 2, 2 versus 3) reached corrected significance at $P < 0.05$. Fig. 2 shows the frequency of perseveration across condition for each patient individually, and illustrates that the trend for reduced perseveration was broadly consistent in each case. This was examined statistically by fitting a linear trend using regression [13]. The trend measures the association between condition and (logged) perseverations and...
Table 1

Patient group accuracy across the conditions of the cancellation task

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total targets available</th>
<th>Number of targets cancelled (mean S.D.)</th>
<th>Targets remaining un-cancelled as a proportion of the total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>54</td>
<td>20.29 (10.87)</td>
<td>63.78</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>16.14 (6.87)</td>
<td>59.64</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>14.29 (6.95)</td>
<td>47.09</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>11.29 (3.64)</td>
<td>29.46</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>7.43 (0.98)</td>
<td>7.14</td>
</tr>
</tbody>
</table>

is examined by t-tests. This analysis revealed statistically significant effects for six of the seven patients in isolation (t(3) values NR = −4.15, P < 0.05, FY = −5.17, P < 0.05, MN = −3.09, P = 0.54, FY = −16.16, P < 0.001, HJ = −5.82, P < 0.05, CI = −4.05, P < 0.05, RH = −4.88, P < 0.05).

A possible confound—that does not account for perseverations occurring, but may account for the modulation we have observed—lies in the relationship between frequency of perseveration and the absolute number of targets cancelled. It could be argued that the greater the number of cancelled targets, the greater the opportunity to re-visit one of them and, hence, to ‘persevere’. To examine this, we created a perseveration percentage (perseverations/targets cancelled) for each patient (see Table 1). Were this confound a factor, we would broadly expect the perseveration percentage to be constant across the conditions. This was not the case. Repeated measures ANOVA revealed a statistically significant linear decrease in perseveration percentage from the 56- to the 8-target conditions (F(1, 4) = 10.45, P < 0.001) which again conformed to a linear trend (F(1, 6) = 37.14, P < 0.01).

2.2.2. Accuracy

The patients’ accuracy in detecting targets as a proportion of the total targets presented in each condition is shown in Fig. 3. Improvement in accuracy in Experiment 1. The proportion of targets that remained un-cancelled in each condition shown together with the reduction in perseverative responses (the mean values of perseverative responses have been divided by 20 to be accommodated on the same scale).
Removal of information from the left therefore led to significant improvements in accuracy that was mirrored in the reduction of perseverative behaviour. Figs. 2 and 3 shows the proportion of un-cancelled targets across the conditions together with the mean number of perseverations made by the group (the number of perseverations has been divided by 20 to be accommodated on the same scale).

In Experiment 1, all stimuli (targets and distracters) were progressively removed from the left. In Experiment 2, we examine whether the reduction in perseveration occurs because of the absence of information in general from the left, or whether the effect is specific to the presence of targets.

3. Experiment 2

3.1. Method

3.1.1. Participants

The same seven patients were tested approximately 1 week after the previous assessment. One, FY, no longer showed neglect for left-sided stimuli nor perseverative behaviour (many patients who show neglect during the acute post-stroke phase rapidly recover in this respect [31]) and was excluded from the new study.

3.1.2. Materials

To examine, whether the effects were specific to left-sided targets we developed a new set of cancellation measures. In condition one, 48 black targets (7 mm × 7 mm stars) were distributed across a white A4 sheet amid 60 distracters (moons, flags, letters and words). In five other conditions, targets were progressively removed from the left of the sheet leaving ultimately only a strip of eight targets at the far right (the number of targets in each being 48, 40, 32, 24, 16 and 8—see Fig. 4). Removed targets were replaced with an additional distracter selected at random from the distracter set, leaving the total number of stimuli on each page constant.

3.1.3. Procedure

Each patient completed all of the conditions in a random order within a single session. Administration was effectively identical to that of Experiment 1, with patients being asked to cross out all of the small star targets and declare when the task was complete.

3.2. Results

3.2.1. Perseverations

As shown in Fig. 4, the results from the remaining six patients strongly suggest that it is the presence of left-sided targets that contributed to the perseveration effect. From making a mean of 14.5 (S.D. = 9.67) perseverations on the 48-target condition, perseverations declined to 0.33 (S.D. = 0.52) on the 8-target condition despite the same number of stimuli being presented on the page as a whole (the number of perseverations in the intervening conditions were 8.17 (S.D. 4.75), 6.17 (S.D. 5.64), 5.17 (S.D. 2.71), 2.50 (S.D. 3.02), respectively). A repeated measures ANOVA with condition as levels of the factor and logged perseveration frequency as the dependent variable confirmed a statistically significant effect (F(1, 5) = 12.61, P<0.001) with no deviation from a linear trend (F(1, 5) = 65.35, P<0.001).

As with Experiment 1, this overall result was considered in more detail using t-test comparisons between each condition. In line with the broadly linear decrease in perseverations, only comparisons between the 48-target condition and the 16- and 8-target conditions reached the necessary P<0.003 levels of significance for 15 comparisons (Holm’s correction—see Experiment 1).

Individual t-tests on association between condition and perseverations revealed significant effects for five of the six targets.
patients considered in isolation (t(4) values NR \(-3.33, P < 0.05\), MN \(-2.85, P < 0.05\), FJ \(-1.95, P < 0.123\), HJ \(-4.45, P < 0.05\), CJ \(-4.13, P < 0.05\), RH \(-4.36, P < 0.05\)).

3.2.2. Perseveration percentage

As with Experiment 1, a preservation percentage (perseverations/number of targets cancelled) was calculated and, again, on repeated measures ANOVA this showed a significant decline as the number of left-sided targets was reduced (F(1, 5) = 6.03, P < 0.01) conforming to a linear trend (F(1, 5) = 10.79, P < 0.05).

3.2.3. Accuracy

In the 48-target condition, the patients found a mean of 21.17 targets (S.D. 13.41), that is, just under half of the stimulus array (44%). The best performance was again from MN who detected 40 targets, while the poorest performer (HJ) was only able to detect 5 targets (10.4%). As with the previous study, and despite the total number of stimuli on
the sheet remaining constant, accuracy as a proportion of the total targets available improved: to 47.9% (S.D. 29.34%) in the 40-target condition, 55.73% (S.D. 35.10%) in the 32-target condition, 65.97% (S.D. 29.63%) in the 24-target condition, 64.58% (S.D. 29.22%) in the 16-target condition, and 89.58% (S.D. 20.02%) in the 8-target condition. The results of this study show:

1. That in a sample of patients selected only on the basis of competition from more salient printed stimuli. Given the spatial working memory deficit highlighted by [14,34] patients might quite legitimately return to and re-mark previously un-cancelled targets without this being considered perseverative.

2. In Experiment 1, a standard cancellation task was modified to create four additional conditions in which targets (and distracters) were progressively removed from the left. Within-subject analysis of performance on the randomly ordered conditions showed that the frequency of perseverative responses was highly modulated by this removal and showed a linear decline. Conversely, accuracy, defined by the proportion of available targets that were cancelled, showed a significant linear increase.

3. In Experiment 2, targets were again progressively removed from the left side of a cancellation sheet, creating seven randomly ordered conditions. In this case, the total number of stimuli (and spatial extent of the stimuli field) was maintained through replacement of removed targets with an additional distracter. As with Experiment 1, a significant reduction in right-sided perseverative responses accompanied this progressive replacement. Also as with Experiment 1, a significant increase in accuracy was observed.

4. Analysis shows that the reduction in perseverance is not simply related to ‘reduced opportunity’ occasioned by the removal of targets. The perseverative percentage (the number of perseverations observed as a proportion of the targets available) also showed a significant linear decline.

5. The accuracy performance on the two conditions in which targets were distributed across the full extent of the page shows that, as a group, the patients were failing to detect the vast majority of targets in the left-half of the sheet. Despite this, the removal of targets within this neglected area and beyond, and the consequent increase in accuracy or ‘task completeness’, was closely mirrored in the reduction in perseverative responses.

In the Introduction, we raised a number of general possibilities that might account for perseverative responses in neglect patients. The first was that patients could have difficulty seeing their own cancellation masks (possibly because of competition from more salient printed stimuli). Given the spatial working memory deficit highlighted by [14,34] patients might quite legitimately return to and re-mark previously un-cancelled targets without this being considered perseverative. The fact that perseverative responses were all but abolished in the extreme right-sided target conditions, however, most particularly in study 2, where the competition from surrounding objects was maintained, makes this account very hard to sustain in a simple form (indeed, it is possible that perseverative responses may have been a factor when patients returned to previously visited targets in these visual-search studies [14,34]).

A second possibility was that patients are showing a form of perseveration that, while clearly co-occurring with neglect, may be a somewhat separable disorder—possibly relating to compromised frontal function. The absence of a relationship between neglect severity and propensity to perseverate reported in [29] is consistent this view. Rusconi et al. suggest that the convergence of a frontally based perseverative disorder with a neglect-based attraction to the right-side of space may account for this behaviour. Clearly, for a stimulus to be on the ‘right’ it requires something to be on the right of—either in the form of reference frame or a stimulus array. If this is the case, our results suggest that the reference frame defined by the paper sheet is generally insufficient to produce these right-sided perseverations. Instead, the behaviour appears in some way reactive to the stimulus field—and in particular, targets, on the ‘left’.

This specificity suggests that the patients (or the mechanisms that determine perseveration) ‘know’ about these left targets—and yet they fail to cancel them. There are a number of existing mechanisms, associated with unilateral neglect, which may account for this curious finding. Neglect can have dissociable sensory and motor components [21,15]. It is possible, therefore, that patients are consciously aware that there are targets to the left of the sheet but are unable to reach into left-space in order to cancel them, and that the action is displaced or transposed onto right-sided targets. The fact that patients do not report such a difficulty (and indeed declare the task complete) is somewhat against this account, but it may, nevertheless, be a factor.

An alternative account stems from previous observations (for example, priming studies [1,18]) that the behaviour of neglect patients can be influenced by left-sided stimuli that they are unable to ostensibly identify or detect (in the sense producing a verbal report). It may be, therefore, that a ‘covert awareness’ of un-cancelled targets on the left produces a sense that the task is incomplete—a sense that drives patients to continue making responses in the only region they
have available to them, the right. A related account is that patients do have a conscious perception of the left-sided targets (perhaps those immediately to the left of the main area of their current inspection) but that they rapidly become confused about the location, or that this experience is directly translated to the good field (a form of anosognosia [12]). For the latter to be the case it would be necessary to posit that the transferred experience becomes attached to existing right sided target locations (the tasks we used did not have symmetrical target locations around the central axis and very few ‘cancellations’ in empty space were performed). The results from the current study do not clearly argue in favour of one or other of these accounts and further work is clearly required.

Previous work has shown that this form of perseveration is closely associated with neglect. However, the implication of these previous findings appears to be that perseveration is not a necessary consequence of neglect, and that neglect is not a necessary consequence of this type of perseveration (see particularly [29]).

Neglect is a notoriously heterogeneous disorder that can arise following damage to a variety of brain structures [28]. In persistent form it is also associated with poor recovery and outcome (e.g. [6,8,25]). Whether or not the tendency to perseverate on the right has a role in the clinical consequences or maintenance of the disorder remains an open question.

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