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You never know where you are going until you know where you have been: Disorganized search after stroke

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Disorders in spatial exploration can be expressed in a disorganized fashion of target cancellation. There is debate regarding whether disorganized search is related to stroke in general, to right brain damage or to unilateral spatial neglect (USN) in particular. In this study, 280 stroke patients and 37 healthy control subjects performed a computerized shape cancellation test. We investigated the number of perseverations and several outcome measures regarding disorganized search: *Consistency* of search direction (best *r*), *distance* between consecutive cancelled targets and *intersections* with paths between previous cancelled targets. We compared performance between patients with left and right brain damage (L, R) and with and without USN (USN+, USN−), resulting in four subgroups: LUSN−, RUSN−, LUSN+, and RUSN+. Higher numbers of intersections were found for the left brain- and right brain-damaged patients with USN and for the right brain-damaged patients without USN, compared to healthy control subjects. Furthermore, right brain-damaged patients with USN showed a higher number of intersections compared to right brain-damaged patients without USN and compared to left brain-damaged patients with USN. To conclude, disorganized search was most strongly related to the neglect syndrome, and patients with more severe USN were even more impaired.

Cancellation tests are widely used to detect unilateral spatial neglect (USN) in stroke patients, as they are the most sensitive among pencil-and-paper tests (Halligan, Marshall, & Wade, 1989; Machner, Mah, Gorgoraptis, & Husain, 2012). In cancellation tests, participants have to mark target shapes that are interspersed with distractors. The number of unmarked targets is a measure of spatial inattention, and a difference of at least two or three omissions between both sides of the stimulus field is generally used as an indication for USN (Mark, Woods, Ball, Roth, & Mennemeier, 2004; Tant, Kuks, Kooijman, Cornelissen, & Brouwer, 2002; Van der Stoep *et al.*, 2013; Wilson, Cockburn, & Halligan, 1987). Thanks to digitalization of neuropsychological tests, more information can be

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gathered from a single test session, and multiple aspects can be analysed. One of them is the organization of search.

Healthy participants typically show organized search strategies when performing a cancellation test. They tend to use one structured, symmetrical pattern, make few errors, and recheck their work (Huang & Wang, 2008; Rabuffetti *et al.*, 2012; Samuelsson, Hjelmquist, Jensen, & Blomstrand, 2002; Warren, Moore, & Vogtle, 2008). Stroke patients show less organized search patterns than healthy participants, either during visual search tests (Chédru, Leblanc, & Lhermitte, 1973) or cancellation tests (Chatterjee, Mennemeier, & Heilman, 1992; Donnelly *et al.*, 1999). Several attempts have been made to investigate whether, and to what extent, search organization is altered in stroke patients in general, or in stroke patients with either right brain damage or USN in particular (Donnelly *et al.*, 1999; Mark *et al.*, 2004; Potter *et al.*, 2000; Rabuffetti *et al.*, 2012; Samuelsson *et al.*, 2002; Weintraub & Mesulam, 1988; Woods & Mark, 2007). Measures of search organization include *consistency, distance* and *intersections*.

The *consistency* of the overall search pattern indicates whether one is searching in the same direction during the whole test, for example in a columnar fashion or row after row. The average *distance* between consecutive cancelled targets is based on the rationale that cancelling targets in close proximity would reflect efficient search, whereas cancelling distant targets reflects inefficient search. Finally, the number of *intersections* indicates the amount of crossings with paths between previously cancelled targets. More intersections would reflect less organized search.

There are conflicting results regarding search organization in patients with left and right brain damage or with and without USN. For example, it was found that patients with right brain damage searched in more directions (thus less consistent) compared to patients with left brain damage (Weintraub & Mesulam, 1988). Studies relating disorganized search to USN have only included right brain-damaged patients, because USN is more severe and persisting in patients with damage to the right hemisphere (Stone, Halligan, & Greenwood, 1993). Patients with USN searched more often from right to left than healthy control subjects (Donnelly *et al.*, 1999; Rabuffetti *et al.*, 2012). However, this does not imply *disorganized* search. In a verbal visual scanning test, right brain-damaged patients with USN read shorter sequences of symbols and made more shifts between scanning by column, by row, and diagonally, compared to right brain-damaged patients without USN, which indicates less consistent search (Samuelsson *et al.*, 2002). However, Mark *et al.* (2004) saw no relation between overall search direction and USN severity. Additionally, no difference in *distance* between consecutive cancelled targets was observed between patients with and without USN (Mark *et al.*, 2004; Rabuffetti *et al.*, 2012). In one study, right brain-damaged patients with USN showed a higher number of *intersections* with paths between previous cancelled targets compared to right and left brain-damaged patients without USN (Rabuffetti *et al.*, 2012), although no relation between the number of *intersections* and USN severity was found in another (Mark *et al.*, 2004).

Comparisons between stroke patients and healthy control subjects in general (Woods & Mark, 2007) provide no information regarding the role of lesion side or USN in disorganized search. By including solely right brain-damaged patients, valuable information is missed, because presumably differences exist between left brain- and right brain-damaged patients regarding search organization (Weintraub & Mesulam, 1988). Furthermore, previous studies included small samples of patients (Mark *et al.*, 2004; Samuelsson *et al.*, 2002; Weintraub & Mesulam, 1988), used a limited number of targets (Donnelly *et al.*, 1999), used non-computerized observations (Mark *et al.*, 2004;

Samuelsson *et al.*, 2002; Weintraub & Mesulam, 1988), or looked at a restricted number of measures (Potter *et al.*, 2000; Weintraub & Mesulam, 1988). In conclusion, there is no consensus yet whether right brain damage, USN, or both are related to disorganized search, and what outcome measure specifies organizational problems in stroke patients the best.

In this study, a computerized version of a shape cancellation test was used, which allowed calculating several standardized measures for search organization in a large sample of participants. Our aim was to investigate whether the number of perseverations and spatial organization measures (i.e., *consistency* of search direction, *distance,* and *intersections*) were related to stroke in general, right brain damage, or USN. First, we compared stroke patients with left or right brain damage and with or without USN versus healthy control subjects. Secondly, we compared the left with the right brain-damaged patients, within the USN subgroups. Finally, we compared patients with USN versus patients without USN within the left brain- and right brain-damaged patient subgroups.

Methods

Participants

Participants consisted of stroke patients who were admitted for inpatient rehabilitation from November 2011 to June 2014 in De Hoogstraat rehabilitation centre. We screened patients according to the following inclusion criteria: (1) clinical diagnosed symptomatic stroke, first or recurrent, verified by magnetic resonance imaging (MRI) and/or computed tomography (CT) data; (2) no severe deficits in communication and/or understanding; (3) normal or corrected to normal visual acuity; (4) and the ability to perform the digitalized shape cancellation test (i.e., able to respond using a computer mouse and understand instructions). We excluded patients with bilateral damage. Patients were also tested with a standard neuropsychological screening, encompassing all cognitive domains. None of the patients had visual agnosia. There was no documentation of ataxia. We did not systematically assess visual field defects and (visual) extinction for this study, because patients with such deficits were included and no further distinction was made. Additionally, we included 37 healthy controls among relatives of the staff, and they were given reimbursement of expenses. The research and consent procedures were in accordance with the standards of the Declaration of Helsinki.

We reviewed the patient's medical record and captured the following admission to rehabilitation data: Gender, age, lesion side, time post-stroke in days, global cognitive functioning score (Mini Mental State Examination, MMSE; Folstein, Folstein, & McHugh, 1975), level of independence during ADL (Barthel Index, BI; Collin, Wade, Davies, & Horne, 1988), strength in the arm and leg (Motricity Index, MI; Collin & Wade, 1990), and the presence of language communication deficits (SAN, 'Stichting Afasie Nederland' score). The mean values of the demographical and stroke characteristics are depicted in Table 1 for each group.

Procedure and tests

All patients were screened on USN using a shape cancellation and line bisection test, as usual care within the first 2 weeks after admission to the rehabilitation centre. USN is a

Table 1. Mean scores and standard deviations at demographical and stroke characteristics among the five groups based on the shape cancellation test

	Controls (n = 37)	LUSN− (n = 115)	RUSN− (n = 108)	LUSN+ (n = 18)	RUSN+ (n = 39)
Gender (% male)	51.35	64.35	58.33	44.44	61.54
Age	44.05 (20.10)	59.14 (10.87)	59.01 (11.89)	59.50 (14.23)	58.23 (13.57)
Days post-stroke	–	32.92 (36.72)	38.39 (58.46)	24.22 (14.44)	50.03 (40.40)
MMSE	–	24.92 (4.57)	27.24 (3.05)	24.14 (4.60)	25.67 (3.68)
BI	–	13.35 (5.50)	12.51 (5.21)	11.00 (5.24)	11.90 (4.78)
MI Arm	–	63.41 (39.00)	65.15 (36.71)	67.50 (39.94)	51.04 (40.22)
MI Leg	–	69.44 (34.65)	72.36 (30.39)	72.08 (35.42)	62.42 (36.48)
SAN	–	4.52 (2.06)	6.31 (1.04)	3.92 (1.94)	5.96 (1.29)
Omissions difference score	0.08 (0.71)	0.23 (0.43)	0.20 (0.41)	4.50 (5.78)	5.82 (5.27)
Line bisection (% USN+/USN−/not finished)	–	26/57/17	38/46/16	39/33/28	85/7.5/7.5
Line bisection (average deviation in deg)	−0.15 (0.24)	−0.39 (0.91)	−0.10 (0.56)	−0.32 (0.88)	1.03 (1.72)

MMSE, Mini Mental State Examination; BI, Barthel Index; MI, Motricity Index; SAN, Stichting Afasie Nederland.

heterogeneous disorder and several processes are involved, which can be measured with different tests (Ferber & Karnath, 2001). We therefore determined the presence of USN first based on results of the shape cancellation test and then again based on results of the line bisection test. Furthermore, the latter test was not directly related to the search organizational measures. The order of the tests was randomized across participants. Participants were seated in front of a monitor at 120 cm. Participants had to use a computer mouse to click at stimuli on the screen.

Shape cancellation test

The shape cancellation test consisted of 54 small targets (0.6° × 0.6°), 52 large distractors, and 23 words and letters (widths ranging from 0.95 to 2.1° and heights ranging from 0.45 to 0.95°). The stimulus presentation was approximately 18.5° wide and 11° high. Participants had to click all targets and tell the examiner when they completed the test. No time limit was given. After each mouse click, a small circle appeared at the clicked location and remained on screen.

Patients with a difference score of two or more omissions between the two sides of the screen were assigned to either the left brain damage (LUSN+) or right brain damage (RUSN+) USN group. The other patients were assigned to the left brain-damaged (LUSN−) or right brain-damaged (RUSN−) group without USN.

Line bisection test

Three horizontal lines (22° long and 0.2° thick) were presented upper right, lower left, and in the horizontal and vertical centre of the screen. The amount of horizontal shift between lines was 15% of the line length. The stimulus presentation was approximately 19° wide and 5.7° high. Participants were asked to click on the subjective mid-point. The three lines were presented four times in a row, after which for each line the average deviation from the mid-point was calculated. The cut-off scores per line were defined as the mean deviation plus three standard deviations of performance of 28 healthy participants (Van der Stoep *et al.*, 2013).

Patients who showed an average deviation that was larger than the cut-off score at one of the three lines were reassigned to one of the USN+ subgroups. The other patients were reassigned to one of the USN− subgroups. Percentages of these groups and the average deviations per group are depicted in Table 1.

Outcome measures

The outcome measures of the shape cancellation test consisted of a time series including, for each click, the time of occurrence of the event and the horizontal and vertical screen coordinates of the clicked location. The original click coordinates within a radius of 50 pixels from the closest target were transformed into the target designated coordinates. Clicks at distractors or at random locations were not used for further analyses, because interpretation of these clicks was difficult. However, observations showed that these clicks were mostly due to either motor problems or inexperience with working with a computer mouse. Two target shapes in the centre were clicked by the examiner as an example and were also not used in analyses. We computed the following shape cancellation scores using all clicks on targets:

- *Omissions difference score*: The difference between the number of omissions between both sides of the screen.
- *Perseverations*: The number of non-consecutive perseverations, that is, number of targets clicked again after at least one other target clicked.

The following *organizational* measures were computed:

- *Consistency of search direction*: The Pearson correlation coefficient (r) from the linear regression of the x- or y-values of all marked locations relative to the order in which they were marked. The highest absolute correlation of these two was selected to represent the degree to which calculations were pursued orthogonally (Mark *et al.*, 2004).
- *Distance*: The average of the Euclidian distances between consecutive clicks to targets.
- *Intersections*: The number of lines that crossed one or more paths between previous cancelled targets divided by the number of total possible intersections.

We computed the *organizational* measures (consistency, distance, and intersections) without the targets that were clicked as a consequence of rechecking, because the organizational measures can be negatively influenced by targets that are omitted in the first place but corrected afterwards (i.e., more intersections are made, the distance is larger, and the search direction is less consistent). We calculated the distances between the last five targets and removed each target and all consecutive targets from analyses in case the distance from the previous target was larger than the mean distance plus two standard deviations of the whole test. The last four clicks to targets were still taken into account in calculating the omissions difference score and number of perseverations. In computing the organizational measures, we included the perseverations in analyses.

Statistical analysis

The distribution of all variables was checked for normality by plotting histograms and computing *Z*-scores for skewness and kurtosis. These calculations showed that the data were not normally distributed, so nonparametric tests were used.

The demographical characteristics (gender and age) were compared between the five groups (i.e., LUSN−, RUSN−, LUSN+, RUSN+, and the healthy control group) with a Kruskal–Wallis nonparametric ANOVA. Furthermore, the stroke characteristics and admission to rehabilitation data (days post-stroke, MMSE, BI, MI Arm, MI Leg, and SAN) were compared between the four stroke subgroups with a Kruskal–Wallis test. Post-hoc Mann–Whitney *U*-tests were performed.

Regarding the different shape cancellation scores (omission difference score, perseverations, *consistency*, *distance,* and *intersections*), we compared each of the four stroke subgroups with the healthy control group, to explore whether the specific subgroups deviated from normal search. Hence, we performed four Mann–Whitney *U*-tests per outcome measure. A Bonferroni correction was applied to avoid a family wise error rate (adjusted level of significance for four tests per measure = .0125).

Second, we analysed whether the side of the lesion accounted for differences in search organization, by comparing LUSN− with RUSN− patients and LUSN+ with RUSN+ patients. Further, we examined the role of USN in disorganized search, by comparing LUSN− with LUSN+ patients and RUSN− with RUSN+ patients (adjusted level of significance for four tests per measure = .0125).

The omission difference score was used as an indication for neglect severity. For the patients with USN+, correlations between the omission difference score and the four outcome measures (perseverations, *consistency*, *distance,* and *intersections*) were calculated using Spearman correlations. Spearman's rho was interpreted as small (>.1), moderate (>.3), large (>.5), or very large (>.7; Dancey & Reidy, 2004).

Finally, patients were regrouped based on performance on the line bisection test. The differences of the LUSN− versus LUSN+ group and RUSN− versus RUSN+ group were examined using two Mann–Whitney *U*-tests (adjusted level of significance for two tests per measure = .025).

Results

Demographic and stroke characteristics

In our sample of 280 patients, 26.53% of right and 13.53% of left brain-damaged patients showed USN. The stroke subgroups and healthy control group were comparable regarding gender distribution, $\chi^2(4) = 3.952, p = .413$. However, the five groups differed on age, $\chi^2(4) = 18.876, p = .001$. All stroke subgroups had a higher age compared to the control group (LUSN−: $U = 1190$, $Z = -4.027$, $p < .001$; RUSN−: $U = 1132$, $Z = -3.929$, $p < .001$; LUSN+: $U = 179.5$, $Z = -2.755$, $p = .006$; RUSN+: $U = 424$, $Z = -3.093$, $p = .002$).[1] No differences existed between the four stroke subgroups (U = 926 to 6,155, Z = −0.717 to −0.110, p = .473–.913). The average ages in years were 44.05 (SD = 20.10) for the healthy control group, 59.14 (SD = 10.87) for the

[1] *To investigate whether the difference in age between the groups could account for potential results, we correlated age with the different measures within the healthy control group. None of the measures were significantly related with age (omissions:* r = *.28,* p = *.095; perseverations:* r = *.06,* p = *.707; best r:* r = *−.08,* p = *.638; distance:* r = *.27,* p = *.101), although a trend was found for age and number of intersections (*r = *.31,* p = *.064).*

LUSN− group, 59.01 (SD = 11.89) for the RUSN− group, 59.50 (SD = 14.23) for the LUSN+ group, and 58.23 (SD = 13.57) for the RUSN+ group.

The stroke subgroups differed regarding the number of days post-stroke onset, $\chi^2(3) = 11.804$, $p = .008$. On average, patients with RUSN+ were tested 26 days later than patients with LUSN+ ($U = 190.5$, $Z = -2.757$, $p = .006$) and 12 days later than patients with RUSN− ($U = 1524.5$, $Z = -2.552$, $p = .011$), whereas the other subgroups did not differ from each other (LUSN+ vs. LUSN−: $U = 797.5$, $Z = -1.516$, $p = .129$; LUSN− vs. RUSN−: $U = 6.057$, $Z = 0.114$, $p = .909$).

Furthermore, the stroke subgroups differed regarding MMSE score, $\chi^2(3) = 16.189$, $p = .001$. The RUSN− group had a higher MMSE score compared to the LUSN− group ($U = 1{,}938$, $Z = -3.525$, $p < .001$) and compared to the RUSN+ group ($U = 814$, $Z = -2.552$, $p = .011$). No differences were observed between the LUSN− and LUSN+ group ($U = 184.5$, $Z = -1.516$, $p = .129$), nor between the LUSN+ and RUSN+ group ($U = 73$, $Z = -0.925$, $p = .355$).

The groups were comparable regarding BI, $\chi^2(3) = 3.555$, $p = .314$; MI arm, $\chi^2(3) = 3.200$, $p = .362$; and MI leg, $\chi^2(3) = 1.580$, $p = .664$.

Finally, a difference was observed in SAN score, $\chi^2(3) = 47.830$, $p < .001$. The LUSN− group obtained a lower SAN score compared to the RUSN− group ($U = 1{,}938$, $Z = -6.128$, $p < .001$), and the LUSN+ group obtained a lower score compared to the RUSN+ group ($U = 71$, $Z = -3.205$, $p = .001$), indicating more severe language communication deficits in the left brain-damaged patients. No differences in SAN score were seen between the LUSN− and LUSN+ group ($U = 496.5$, $Z = -1.004$, $p = .315$) nor between the RUSN− and RUSN+ group ($U = 1005.5$, $Z = -1.444$, $p = .149$).

Search organization measures

In Table 2, the shape cancellation outcome measures are depicted for all groups. Differences existed between the five groups regarding the omission difference score, $\chi^2(4) = 198.272$, $p < .001$; number of perseverations, $\chi^2(4) = 10.032$, $p = .040$; *consistency* of search direction, best r; $\chi^2(4) = 11.291$, $p = .023$; *distance* between consecutive cancelled targets, $\chi^2(4) = 51.759$, $p < .001$; and number of *intersections,* $\chi^2(4) = 50.018$, $p < .001$. Box plots for the organizational measures are depicted in Figure 1.

Stroke patients versus healthy controls

Compared with the healthy control group, the LUSN+ ($U = 0.00$, $Z = -6.871$, $p < .001$) and RUSN+ group ($U = 0.00$, $Z = -7.876$, $p < .001$) omitted more targets. No difference

Table 2. Mean scores and standard deviations at the organizational measures among the five groups based on the shape cancellation test

	Controls (n = 37)	LUSN− (n = 115)	RUSN− (n = 108)	LUSN+ (n = 18)	RUSN+ (n = 39)
Perseverations	0.22 (0.71)	0.41 (0.99)	0.50 (2.41)	1.72 (3.10)	0.92 (1.95)
Best r	.88 (.12)	.84 (.18)	.79 (.22)	.78 (.22)	.77 (.20)
Distance	139 (44)	154 (38)	159 (15)	167 (49)	202 (66)
Intersections	.03 (.05)	.05 (.06)	.06 (.06)	.07 (.05)	.14 (.12)

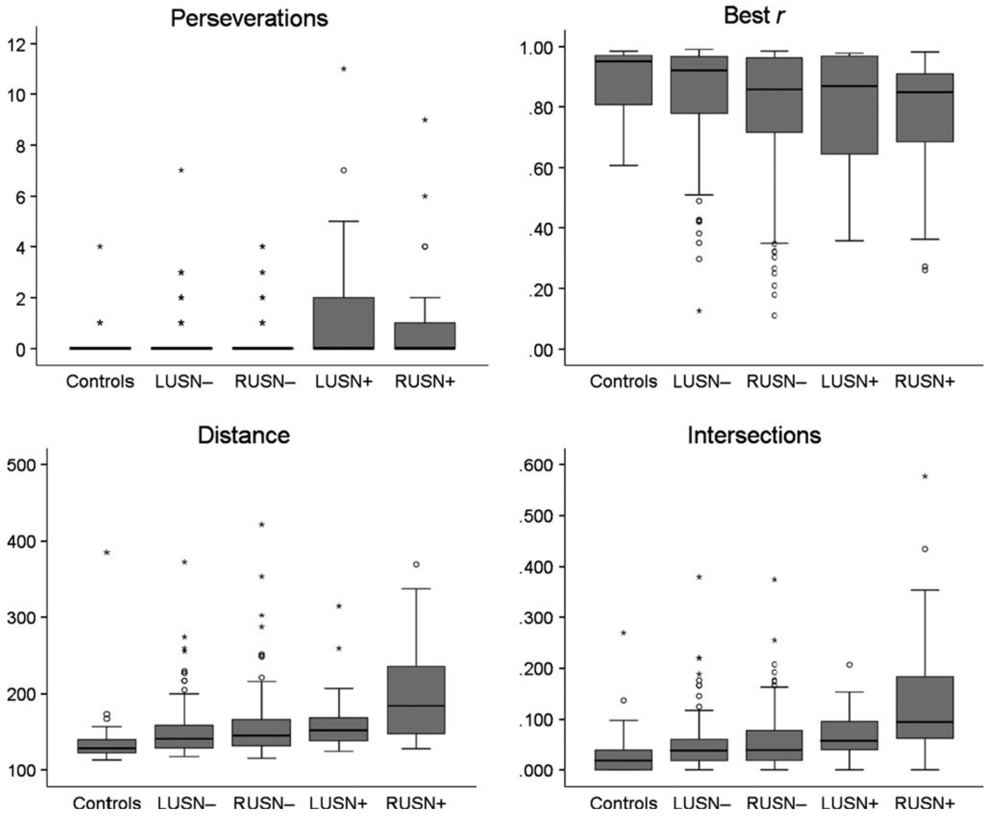

Figure 1. Box plots for the number of perseverations, best *r*, distance, and number of intersections. Median, quartiles, extreme values, and outliers are depicted.

in number of omissions was seen for the LUSN− (U = 1800.5, Z = −2.036, p = .042) and RUSN− group (U = 1753, Z = −1.698, p = .089) compared with the healthy control group.

The number of perseverations did not differ between the stroke subgroups and the healthy control group (U = 238.5–1,926, Z = −2.349 to −0.514, p = .019–.607).

Furthermore, the *consistency* of the search direction did not differ between the LUSN−, RUSN−, and LUSN+ groups (U = 248–1,914, Z = −2.036 to −0.917, p = .042–.359) versus the healthy control group. Only the RUSN+ group showed a less consistent search direction compared to the healthy control group (U = 472, Z = −2.593, p = .010).

All stroke subgroups showed a larger *distance* between consecutive cancelled targets compared with the healthy control group (U = 125–1186.5, Z = −5.950 to −3.731, p < .001).

In the RUSN−, LUSN+, and RUSN+ groups, a higher number of *intersections* was observed compared with the healthy control group (U = 169–1282, Z = −5.708 to −2.997, p < .003). The number of intersections of the patients with LUSN− did not differ from the healthy control patients (U = 1630, Z = −2.164, p = .030).

Table 3. Comparisons of the search organizational measures between left brain- and right brain-damaged patients

	LUSN− vs. RUSN−	LUSN+ vs. RUSN+
Omissions difference score	$U = 6{,}017, Z = -0.939, p = .576$	$U = 216, Z = -2.384, p = .017$
Perseverations	$U = 5{,}899, Z = -0.939, p = .348$	$U = 312, Z = -0.799, p = .424$
Best *r*	$U = 5{,}276, Z = -1.940, p = .052$	$U = 324, Z = -0.464, p = .643$
Distance	$U = 5770.5, Z = -0.913, p = .361$	$U = 224, Z = -2.180, p = .029$
Intersections	$U = 5433.5, Z = -1.621, p = .105$	$U = 198, Z = -2.629, p = .009$*

*Significant with the adjusted level of significance ($\alpha = .0125$).

Left versus right brain-damaged patients

Statistics for these comparisons are depicted in Table 3. The LUSN− group omitted as many targets as the RUSN− group ($p = .576$). However, the RUSN+ group tended to omit more targets than the LUSN+ group, although this was not statistically significant ($p = .017$). This trend could indicate that patients in the RUSN+ group showed more severe USN compared with patients in the LUSN+ group.

The number of perseverations was comparable between the LUSN− and RUSN− group ($p = .348$) and between the LUSN+ and RUSN+ group ($p = .424$).

No difference was seen regarding the *consistency* of search direction between the LUSN− and RUSN− group ($p = .052$) nor between the LUSN+ and RUSN+ group ($p = .643$).

The *distance* between the consecutive cancelled targets did not differ between the LUSN− and RUSN− group ($p = .361$), nor between the RUSN+ group versus the LUSN+ group ($p = .029$).

The LUSN− and RUSN− group showed a comparable number of *intersections* ($p = .105$), whereas the RUSN+ group showed a higher number of intersections compared to the LUSN+ group ($p = .009$).

USN+ versus USN− patients (shape cancellation test)

As expected, the LUSN+ patients omitted more targets compared to the LUSN− patients ($p < .001$), and the RUSN+ patients omitted more targets compared to the RUSN− patients ($p < .001$; see Table 4 for statistics).

No difference was seen in amount of perseverations between the LUSN− and LUSN+ group ($p = .057$), nor between the RUSN+ and RUSN− group ($p = .047$). No relation was observed between neglect severity and the number of perseverations ($r = .10$, $p = .484$).

The *consistency* of search direction (best *r*) did not differ between the LUSN+ and LUSN− group ($p = .057$) nor between the RUSN+ and RUSN− group ($p = .298$). Additionally, no relation between neglect severity and consistency of the search direction was found ($r = -.22, p = .104$).

We observed no difference in distance between consecutive clicked targets between the LUSN+ and LUSN− group ($p = .109$). Interestingly, the RUSN+ group showed a larger *distance* between consecutive cancelled targets compared to the RUSN− group ($p < .001$). The distance between consecutive cancelled targets was not related to neglect severity ($r = .20, p = .128$).

Table 4. Comparisons of the search organizational measures between patients with USN+ and USN− (shape cancellation test)

	LUSN− vs. LUSN+	RUSN− vs. RUSN+
Omissions difference score	$U = 0.00, Z = -8.128, p < .001$*	$U = 0.00, Z = -10.357, p < .001$*
Perseverations	$U = 818.5, Z = -8.128, p = .057$	$U = 1{,}787, Z = -1.990, p = .047$
Best *r*	$U = 908, Z = -1.902, p = .057$	$U = 1{,}869, Z = -1.040, p = .298$
Distance	$U = 791.5, Z = -1.602, p = .109$	$U = 1{,}120, Z = -4.326, p < .001$*
Intersections	$U = 740, Z = -1.955, p = .051$	$U = 957.5, Z = -5.046, p < .001$*

*Significant with the adjusted level of significance ($\alpha = .0125$).

Again, no difference in number of intersections was seen between the LUSN− and LUSN+ group ($p = .051$), while the RUSN+ group showed a larger number of *intersections* compared to the RUSN− group ($p < .001$). Finally, the number of intersections showed a moderate positive correlation with neglect severity ($r = .34$, $p = .009$).

USN+ versus USN− patients (line bisection test)

Of all patients, 235 also completed the line bisection test. Patients were regrouped based on results of the line bisection test. The mean values of the shape cancellation measures for each new subgroup, and statistics of the comparisons are depicted in Table 5.

Again, the LUSN+ group omitted more targets compared to the LUSN− group ($p = .009$) and the RUSN+ group omitted more targets compared with RUSN− group ($p < .001$).

No difference was seen regarding the number of perseverations between the LUSN+ and LUSN− group ($p = .116$) nor between the RUSN+ and RUSN− group ($p = .723$).

The LUSN− and LUSN+ group did not differ regarding *consistency* of search direction ($p = .074$), whereas the RUSN+ group searched less consistent compared to the RUSN− group ($p = .009$).

The *distance* between consecutive clicked targets was comparable for the LUSN− and LUSN+ groups ($p = .226$) and for the RUSN+ and RUSN− groups ($p = .035$).

Finally, no difference was seen regarding number of *intersections* between the LUSN− and LUSN+ group ($p = .712$), whereas the RUSN+ group showed a larger number of intersections compared with the RUSN− group ($p = .001$).

To summarize, when subgroups were made based on the line bisection test, we observed a difference in search *consistency* between patients with RUSN+ and RUSN−, which was not seen when subgroups were based on the shape cancellation test. Finally, only when subgroups were based on the shape cancellation test, patients with RUSN+ showed a larger distance than patients with RUSN−. The other results confirm the comparison between these subgroups when classification was based on the shape cancellation test.

Table 5. Mean scores and standard deviations at shape cancellation measures and comparisons among the four patient subgroups based on the line bisection test

	LUSN− (n = 75)	LUSN+ (n = 41)	LUSN− vs. LUSN+	RUSN− (n = 61)	RUSN+ (n = 80)	RUSN− vs. RUSN+
Omissions difference score	0.36 (0.71)	1.68 (4.39)	U = 1161.5, Z = −2.603, p = .009*	0.34 (0.75)	2.71 (4.63)	U = 1,469, Z = −4.504, p < .001*
Perseverations	0.37 (1.15)	0.51 (1.00)	U = 1,345, Z = −1.573, p = .116	0.36 (0.90)	0.88 (3.09)	U = 2,380, Z = −0.354, p = .723
Best r	.87 (.18)	.81 (.19)	U = 1,228, Z = −1.787, p = .074	.82 (.20)	.75 (.22)	U = 1,816, Z = −2.597, p = .009*
Distance	155 (43)	158 (34)	U = 1,328, Z = −1.210, p = .226	162 (51)	174 (55)	U = 1,932, Z = −2.114, p = .035
Intersections	.05 (.05)	.05 (.06)	U = 1,474, Z = −0.370, p = .712	.06 (.05)	.10 (.10)	U = 1,646, Z = −3.308, p = .001*

*Significant with the adjusted level of significance (α = .025).

Discussion

Our overall aim was to investigate whether disorganized search was related to stroke in general, or to right brain damage or to USN in particular. To this aim, we used a shape cancellation test and analysed several outcome measures related to search organization: (1) *consistency* of search direction, (2) *distance* between consecutive cancelled targets, and (3) number of *intersections* with paths between previous cancelled targets. We compared performance between patients with left and right brain damage (L, R) and with and without USN (USN+, USN−) based on the shape cancellation test, resulting in four subgroups: LUSN−, RUSN−, LUSN+, and RUSN+. First, we compared the subgroups with healthy control subjects, and it was found that all four subgroups were on average 15 years older than the healthy control subjects. There is some evidence that age affects visual search (Müller-Oehring, Schulte, Rohlfing, Pfefferbaum, & Sullivan, 2013), but this is mainly related to decline in speed rather than search organization (Geldmacher & Riedel, 1999). We analysed the scores on the organizational measures in relation to age in the current study and observed that only the number of *intersections* showed a positive trend correlation. However, the LUSN− group did not differ from the healthy control group on this measure, suggesting that something other than age must account for the differences between the other stroke groups and the healthy control group. Regarding the other measures, all stroke subgroups showed a larger *distance* between consecutive cancelled targets compared to the healthy control group. Finally, only the RUSN+ group searched *less consistent* in comparison with the healthy control group.

Previously it was shown that right brain-damaged patients searched less organized compared to left brain-damaged patients (Weintraub & Mesulam, 1988). However, this could be explained by the fact that presumably more patients with USN were present among the right brain-damaged patients (Stone *et al.*, 1993). By splitting patients on *both* lesion side and USN and comparing these subgroups with each other, we revealed that no differences existed between patients with LUSN− and RUSN−. A difference existed within the patients with USN: The patients with RUSN+ made more omissions, showed a larger distance, and showed a higher number of intersections compared to the patients with LUSN+. Analysing disorganized search in patients with and without USN learned that no differences were seen between the LUSN− and LUSN+ group, whereas the RUSN+ group searched less organized compared to the RUSN− group.

The observation of poorer search organization in patients with RUSN+ compared to patients with RUSN− was replicated when USN groups were determined based on results on the line bisection test. Again, patients with RUSN+ showed a higher number of *intersections* with previous crossed targets compared to patients with RUSN−. These results suggest that patients with RUSN+ searched less organized compared to patients with RUSN−, regardless of the specific type of USN. However, only when patients were classified based on the shape cancellation test, patients with RUSN+ showed a higher *distance* than patients with RUSN−, and only when patients were classified based on the line bisection test, patients with RUSN+ differed regarding *consistency* of search compared to patients with RUSN−. This inconsistent finding could be explained by different cognitive processes underlying performance on each test; cancellation tests have been associated with a more egocentric frame of reference, whereas line bisection may require a combination of both allocentric and egocentric reference frames (Oppenländer *et al.*, 2015). Disturbances of ventral (temporal) information processing, concerning detailed object representations, might lead to allocentric impairment, whereas disorders of the fronto-parietal processing stream, dealing with spatial information, might cause egocentric deficits (Grimsen, Hildebrandt, & Fahle, 2008). Possibly, egocentric deficits resulted in both problems at the line bisection test and less consistent search at the cancellation test.

The different results for the current search organization measures question which of them appears to pinpoint efficient strategy best. The measures of *distance* and *intersections* were previously analysed in a study of Rabuffetti *et al.* (2012), who divided 193 stroke patients in LUSN−, RUSN−, and RUSN+ subgroups and compared them with healthy control subjects. No patients with LUSN+ were present. They observed no differences regarding distance, whereas the number of intersections differed for all groups. The contrary findings regarding distance could be explained by their cancellation template, in which targets were more equally distributed across the stimulus field than in our shape cancellation test, in which targets were distributed in a more columnar fashion (also used by Mark *et al.*, 2004). Both the direction and pattern of the search affected the distance (Figures 2 and 3). The distance was the smallest in case of a ‘snake pattern’ in the vertical direction, and the largest in case of a ‘typewriter pattern’ in the horizontal direction. Thus, in our study, high scores for distance did not necessarily imply disorganized search, as all four possible choices (i.e., horizontal or vertical direction and a snake or typewriter pattern) were structured. However, the distance could tell something about the difference in pattern and direction choice between the stroke patients and healthy control subjects. The most common cancellation path chosen by the healthy

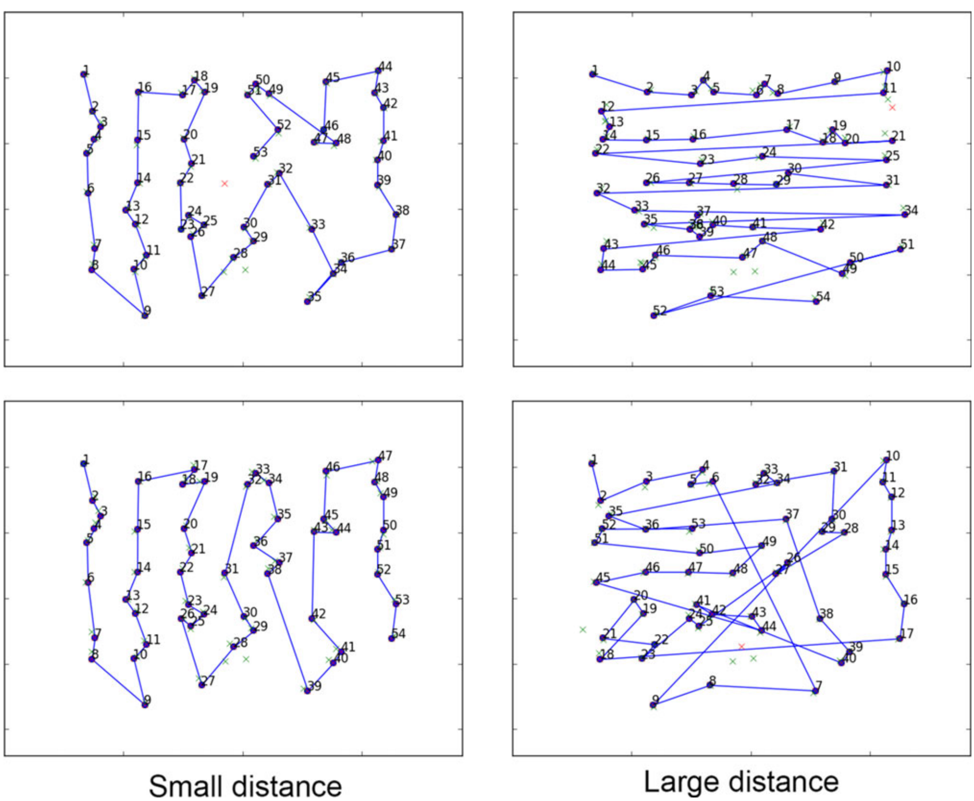

Figure 2. Examples of search patterns resulting in small (left images) or large (right images) distance between consecutive cancelled targets.

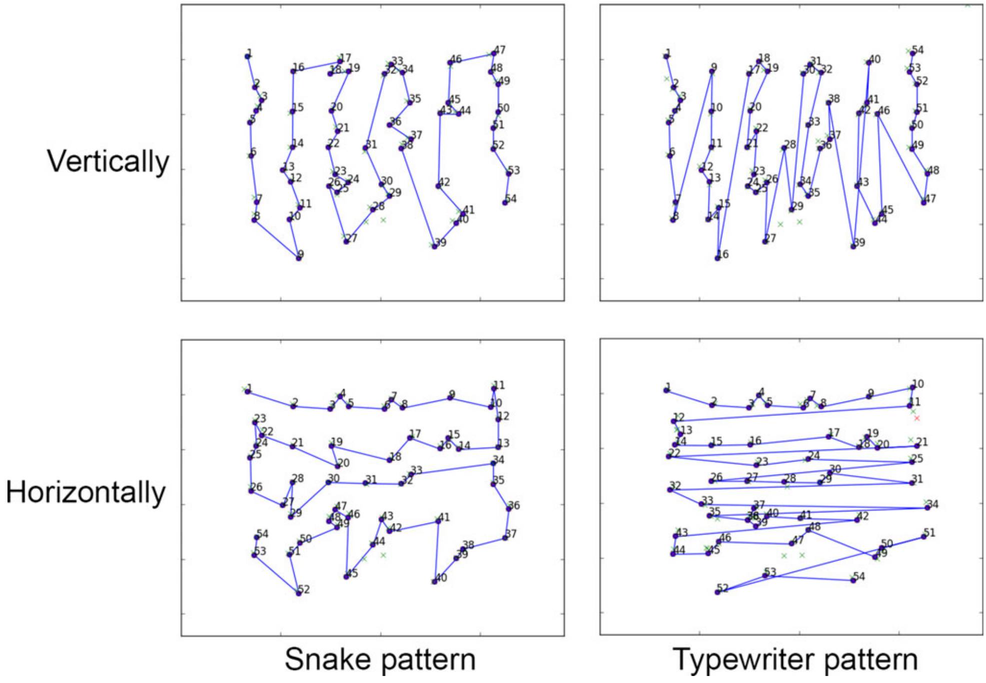

Figure 3. Examples of cancellation directions and patterns. Upper and lower images depict two different search directions and left and right images depict two different search patterns.

control subjects in the study of Rabuffetti *et al.* (2012) was in the horizontal direction. In our study, however, we observed that healthy control subjects choose a 'snake pattern' in the vertical direction most often, and rarely choose a 'typewriter pattern' or the horizontal direction. The patients showed a variety of patterns and directions, which can explain the larger average distance compared to the healthy control group. A possible explanation for the differences in choice of search pattern and direction is that the 'snake pattern' in the vertical direction, which was chosen the most by healthy control subjects, was the most efficient cancellation pattern in our specific test (e.g., consecutive targets were the closest). It is likely that stroke patients in general have more difficulty in obtaining a quick proper overview in (complex) spatial layouts, for example due to slowed information processing and/or executive dysfunction (Cumming, Marshall, & Lazar, 2013; De Haan, Nys, & Van Zandvoort, 2006), resulting in difficulty in choosing the most efficient pattern.

The measure regarding the consistency of search (best *r*) seems to depict whether one is searching in the same direction during the whole test. In case of a cochlear pattern (Figure 4), however, the score is quite low, despite the used pattern is consistent.

Previously, Woods and Mark (2007) reported high convergent validity of the *consistency* of search direction, *distance,* and *intersections*. Despite this finding, we argue that abnormal scores on the first two measures do not *necessarily* imply disorganized search. Both the *distance* and *consistency* seemed confounded by the choice of search direction and pattern.

To summarize, we conclude that the number of *intersections* with paths between previously cancelled targets is the most sensitive measure to indicate problems with

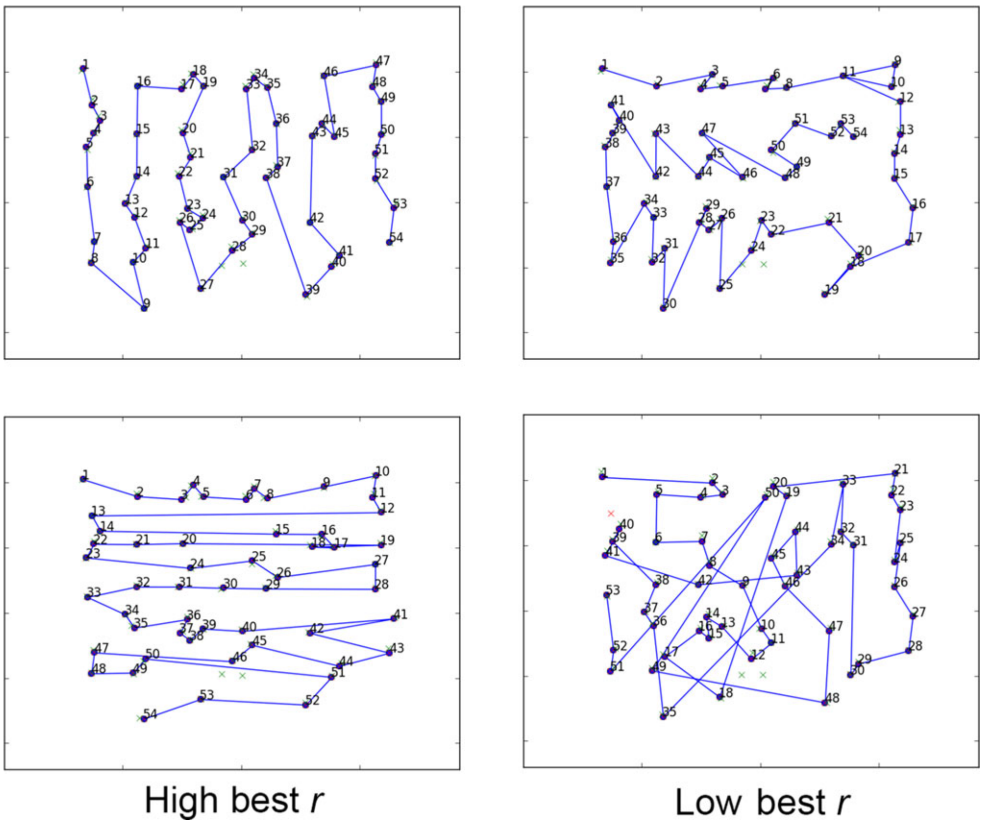

Figure 4. Examples of search patterns resulting in high (left images) or low (right images) values for best *r*.

search organization in a stroke population. This measure reflects the number of path crossings with previous cancellation paths (Figure 5). The number of intersections was higher for patients with RUSN−, LUSN+, and RUSN+ versus healthy control subjects. Despite that the number of intersections was largely comparable between the LUSN− and LUSN+ group, only the patients with LUSN− performed comparable with healthy control subjects. Furthermore, the RUSN+ group showed a higher number of intersections compared with the RUSN− and the LUSN+ group. This could be explained by the observation that patients with right brain damage showed more severe USN compared to patients with left brain damage, and neglect severity was related to the number of intersections. Additionally, the RUSN+ group was tested later than the LUSN+ group and the RUSN− group, indicating that these patients stayed longer at the hospital before being admitted to the rehabilitation centre. It is known from the literature that right brain-damaged patients with USN are more severe affected after stroke than right brain-damaged patients without USN. For example, USN correlated positively with motor function impairment, visual and tactile sensory loss and anosognosia and predicted family burden (Buxbaum *et al.*, 2004). Yet, based on the literature, it seems unlikely that poorer outcome after stroke is the most important factor explaining the results, but instead right hemisphere damage (Weintraub & Mesulam, 1988) accompanied by USN is (Rabuffetti *et al.*, 2012; Samuelsson *et al.*, 2002).

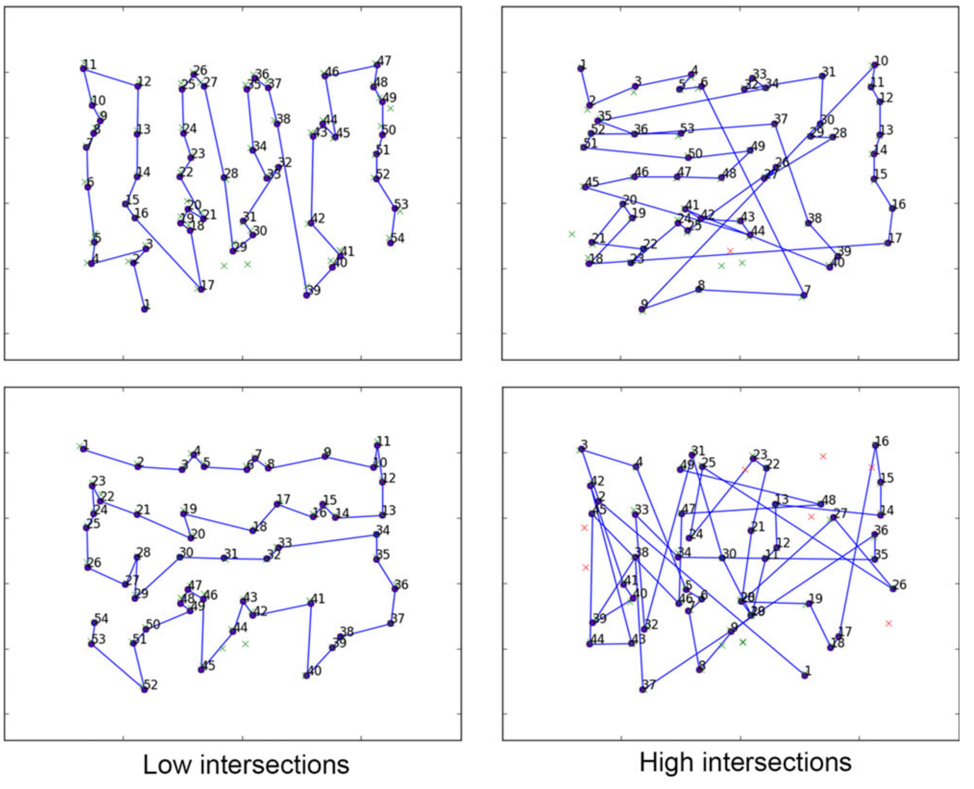

Figure 5. Examples of search patterns resulting in low (left images) or high (right images) values for intersections.

Several cognitive and visuospatial factors may contribute to disorganized search in patients with USN. First of all, patients with USN show a spatial bias of attention to the ipsilesional side. For example, they more often make saccades to the ipsilesional side than to the contralesional side (Ro, Rorden, Driver, & Rafal, 2001). In a subset of patients with USN, spatial working memory could be additionally disturbed, due to right posterior parietal damage (Luukkainen-Markkula, Tarkka, Pitkänen, Sivenius, & Hämäläinen, 2011; Malhotra *et al.*, 2005; Pisella & Mattingley, 2004; Pisella *et al.*, 2011). In a study of Malhotra *et al.* (2005), it was shown that patients with USN were unable to remember whether a spatial location was displayed in a sequence or not. When a patient is unable to keep track of spatial locations during a cancellation test, the same locations will be searched repeatedly, leading to disorganized search. The disturbed underlying mechanism could be spatial remapping, which can be considered as the elementary stage of processing for spatial working memory (Pisella & Mattingley, 2004). At each ocular fixation, the retinotopic maps are renewed in the primary visual areas. The successive maps are integrated in the parietal cortex by remapping processes that provide an updated representation of components of the visual scene. In this way, a stable and spatially relevant representation of the visual scene is maintained (Pisella & Mattingley, 2004). This level of visual space representation is proposed to be located in the right inferior parietal lobule. Damage of the right posterior parietal cortex, including the inferior parietal lobule, disturbs the remapping process. In a normal process of integration, the important information from the previous retinal image is stored and prevented from being overwritten. In case the remapping process is disturbed, the relevant information disappears from awareness and affects the next eye movement (Pisella & Mattingley, 2004; Pisella *et al.*, 2011). In a cancellation test, this could lead to a loss of awareness of targets, even in case these targets were processed earlier during the test. As a consequence, these patients have no clear image of the relative position of targets on the stimulus field. This may cause disorganized search during cancellation tests, expressing in cancelling targets that are distant from each other, changing the cancellation pattern and cross-paths between already cancelled targets.

An impairment of visual remapping could also explain perseverations, whereby the marked targets are overwritten by a new visual scene and treated as new targets (Husain *et al.*, 2001). Perseverations have been associated with USN in some studies (Na *et al.*, 1999; Nys, Nijboer, & de Haan, 2008; Nys, van Zandvoort, van der Worp, Kappelle, & de Haan, 2006), but not in others (Rusconi, Maravita, Bottini, & Vallar, 2002). In the current study, both healthy control subjects and stroke patients without USN showed some preservative responses, which has been observed before (Nys *et al.*, 2006), and no significant differences were found. The distinctness of the circles that appeared around the targets could have prevented patients with USN to revisit targets more often. In tests whereby the marks are less obvious or absent, patients with USN are provoked to perseverate more (Husain *et al.*, 2001).

Conclusion and implications

In the present study, the patients with RUSN+ were less organized compared to the patients with LUSN+ and RUSN−, which was expressed in a higher number of intersections with previous cancellation paths and a larger distance between consecutive cancelled targets. The difference between left brain- and right brain-damaged patients within the USN group seemed primarily caused by the degree of USN, which was more severe in the right brain-damaged patients. Furthermore, whereas the patients with LUSN+ deviated from normal performance regarding the number of intersections, patients with LUSN− performed comparable with healthy control subjects. Thus, disorganized search is in particular related to the neglect syndrome and is even more evident in severe USN, which is related to right brain damage.

Identifying search strategies and degree of search organization might gain insight in visuospatial processes and attention of stroke patients. It is useful to evaluate search organization apart from USN during neuropsychological assessment. Patients who do not show USN but do show disorganized search could experience problems during ADL, such as slowness or inefficient searching for personal belongings. Measures of search organization could already be analysed in standard neuropsychological tests. Currently, free software is available to analyse all kinds of computerized cancellation tests and compute organizational measures (Dalmaijer, Van der Stigchel, Nijboer, Cornelissen, & Husain, 2015). Future research needs to examine whether search organization can be trained during rehabilitation.

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