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Research report

The right hemisphere is dominant in organization of visual search—A study in stroke patients

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HIGHLIGHTS

- Search organization was studied in a large sample of stroke patients.
- Disorganized search (DS) was found in 22% of stroke patients.
- Lesions in right parietal, temporal and occipital areas were related to DS.
- These regions are associated with conjunctive search and spatial working memory.
- Spatial processes appear to be the key mechanisms, compared to frontal functions.

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ABSTRACT

Cancellation tasks are widely used for diagnosis of lateralized attentional deficits in stroke patients. A disorganized fashion of target cancellation has been hypothesized to reflect disturbed spatial exploration. In the current study we aimed to examine which lesion locations result in disorganized visual search during cancellation tasks, in order to determine which brain areas are involved in search organization. A computerized shape cancellation task was administered in 78 stroke patients. As an index for search organization, the amount of intersections of paths between consecutive crossed targets was computed (i.e., intersections rate). This measure is known to accurately depict disorganized visual search in a stroke population. Ischemic lesions were delineated on CT or MRI images. Assumption-free voxel-based lesion-symptom mapping and region of interest-based analyses were used to determine the grey and white matter anatomical correlates of the intersections rate as a continuous measure. The right lateral occipital cortex, superior parietal lobule, postcentral gyrus, superior temporal gyrus, middle temporal gyrus, supramarginal gyrus, inferior longitudinal fasciculus, first branch of the superior longitudinal fasciculus (SLF I), and the inferior fronto-occipital fasciculus, were related to search organization. To conclude, a clear right hemispheric dominance for search organization was revealed. Further, the correlates of disorganized search overlap with regions that have previously been associated with conjunctive search and spatial working memory. This suggests that disorganized visual search is caused by disturbed spatial processes, rather than deficits in high level executive function or planning, which would be expected to be more related to frontal regions.

Abbreviations: FDR, false discovery rate threshold; IFO, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; MMSE, Mini-Mental State Examination; MNI, Montreal Neurological Institute; PCA, posterior cortical atrophy; ROI, region of interest; SAN, Stichting Afasie Nederland; SLF, superior longitudinal fasciculus; VLSM, voxel-based lesion-symptom mapping.

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1. Introduction

Cancellation tasks are widely used for diagnosis of lateralized attentional deficits in stroke patients. In these tasks, multiple targets have to be found among distractors and crossed out. Additionally, cancelled targets should not be crossed out twice. An asymmetry in number of omitted targets between the left versus right half of the page is typically used as an indication for visuo-spatial neglect, an attentional disorder which is defined as the failure to orient, report or respond to visual stimuli toward the contralesional side of space [20].

Completing a cancellation task in an *organized* way requires a preconceived top-down strategy. Though it is achievable to cancel all targets without adopting a specific strategy, a disorganized fashion of target cancellation has been hypothesized to reflect a disorder in spatial exploration or planning [31]. For instance, stroke patients show less organized cancellation patterns compared to healthy control subjects [37,47]. Moreover, stroke patients with visuo-spatial neglect have an even less organized visual search pattern compared to stroke patients without neglect [7,37,43,47,53]. Even though the presence of visuo-spatial neglect seems a marker for a disorganized search pattern in stroke patients, the relation is not straightforward, and neglect and disorganized search seem to be distinct phenomena [31]. Disorganized visual search during cancellation might reflect a multitude of various deficits, such as disturbed executive function, spatial working memory disorder (remapping problems), deficient inhibition of return, loss of a strategy or plan to guide spatial search, difficulties with disengaging attention from already cancelled targets or a failure to inhibit stimulus-bound motor responses [31].

In this study, we aimed to investigate the anatomical correlates of visual search organization. A computerized version of a cancellation task was presented to patients with stroke and used to compute the amount of *intersections* with paths between previous cancelled targets [14,37,47,54]. This measure is thought to best depict organization of visual search in a stroke population [47]. We performed voxel-based lesion-symptom mapping (VLSM) and region of interest-based (ROI) analyses within grey and white matter to determine the anatomical correlates of visual search organization, and to learn about the various components of visual search.

2. Material and methods

2.1. Procedure

The design of this study was retrospective. All clinical tests and imaging were conducted in the setting of standard clinical care. The research and consent procedures were performed in accordance with the standards of the Declaration of Helsinki.

2.2. Participants

Patients were selected from a cohort consisting of 357 stroke patients who were consecutive admitted to De Hoogstraat Rehabilitation center from November 2011 through February 2014. MRI or CT scans were administered in the hospital. At admission to the rehabilitation center, patients were screened for visuo-spatial neglect with a cancellation task as part of usual care within the first two weeks, if their condition permitted testing. A stepwise exclusion procedure was applied to these 357 patients according to the following criteria: (1) no data on the shape cancellation task (i.e., unable to understand instructions or unable to perform the task due to motor problems or fatigue; $n = 31$); (2) diagnosis other than ischemic stroke or delayed cerebral ischemia after subarachnoid haemorrhage ($n = 85$); (3) no delayed CT (i.e., performed >48 h after symptom onset) or MRI brain scan available for infarct segmentation ($n = 154$); (4) no infarct visible on post-stroke imaging ($n = 6$); and (5) insufficient quality of CT or MRI imaging ($n = 2$) (Supplementary Fig. 1).

2.3. Clinical characteristics

The following data were obtained on admission to the rehabilitation center: gender, age, time post-stroke, global cognitive functioning score (Mini-Mental State Examination, MMSE [17]), level of independence during daily live activities (Barthel Index [9]), strength in both upper and lower extremities (Motricity Index [8]), and presence of language communication deficits (Stichting Afasie Nederland, SAN score).

2.4. Shape cancellation task

The computerized shape cancellation task consisted of 54 small targets ($0.6^\circ \times 0.6^\circ$), 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. Patients were seated 120 cm in front of a monitor and used a computer mouse. They were instructed to click all targets and tell the examiner when they had completed the task. No time limit was given. After each mouse click a small circle appeared at the clicked location and remained on screen, regardless whether a target, distractor, or location in between was clicked [51].

For each patient, all cancelled targets were connected in chronological order. Clicks at other locations were excluded from analyses. Targets that were revisited were included in analyses. The amount of crossings of paths between cancelled targets was computed (i.e., intersections). For each participant the *intersections rate* was computed with the CancellationTools software [14]. The intersections rate depicts the total amount of path intersections divided by the amount of cancellations that are not immediate revisits, resulting in a value ranging from 0 (no intersections) to 1 (maximum amount of intersections). An organized search pattern includes as few intersections as possible. That is, a high number of intersections would reflect less organized visual search [37,47]. See Fig. 1 for the target stimuli layout and examples of organized versus disorganized search. The convergent validity of the intersections rate was good, as observer ratings of disorganized search during a cancellation task were highly correlated with the intersections rate ($r = .87$ [54]).

In order to assess the robustness of the VLSM results with the intersections rate as continuous measure, we additionally performed VLSM using norm-based dichotomized performance on the shape cancellation task and a qualitative lesion subtraction analysis. In order to dichotomize the intersections rate, we used the scores of 37 healthy control subjects [47]. The threshold was set at their mean score plus 2.5 standard deviations. Stroke patients with an intersections rate above this threshold were assigned to the disorganized search group, whereas the other stroke patients were assigned to the organized search group.

2.5. Generation of lesion maps

The procedure for the generation of lesion maps has been previously described elsewhere and is only summarised here (for more details see Refs. [3–5]). Infarcts were manually segmented on transversal slices of either follow-up CT ($n = 49$), or on T2 FLAIR sequences of MRI scans ($n = 29$) by a trained rater who was blinded to the cancellation data (JMB). Infarct segmentations were transformed to the Montreal Neurological Institute (MNI)-152 template [18] using the following procedure. All registrations were performed with the elastix toolbox for registration [25]. An age-specific

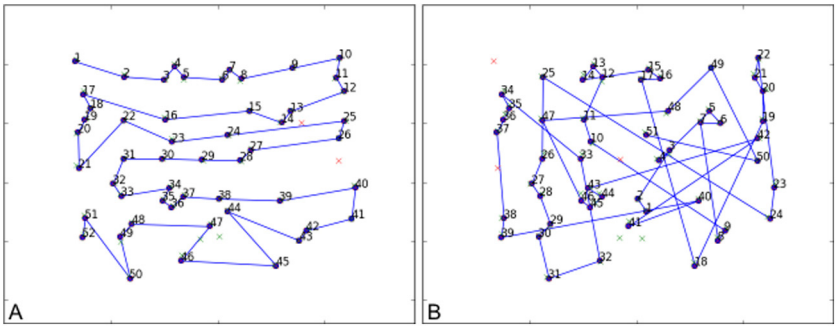

Fig. 1. Examples of search patterns. Search patterns resulting in low (A) or high (B) values for intersections.

brain template was used [39], which included a CT and T1 MRI template in the same coordinate space. T2 FLAIR scans were transformed to their corresponding T1 scan using a linear registration. The T1 scans were transformed to the T1 MRI template, with a linear registration followed by a non-linear registration. The registration of the CT scans to the CT template was performed using an in-house developed algorithm, which is described elsewhere [27]. The age-specific T1 MR template was transformed to the T1 MNI-152 template, with a linear and a non-linear registration. All computed transformations were composed into a single transformation step – transforming from source CT/MRI to template CT/MRI to MNI-152 – that was used to align the infarct maps directly to the MNI-152 template. The intermediate registration step using the age-specific CT/MRI template served to improve the quality of the registration by providing a better match between patient and template. Quality checks of the registration results were performed by comparing the native scan to the lesion map in MNI space. For 44 patients, the co-registered lesion maps were manually adjusted to correct for slight registration errors using MRIcron (http://www.sph.sc.edu/comd/rorden/mricron) by JBM.

2.6. Statistical analysis

First, clinical characteristics of patients who showed a disorganized search pattern were statistically compared to those of patients who showed an organized search pattern, using Mann Whitney tests and a Chi-Square test, since data was not normally distributed. Additionally, the lesion locations between the groups with organized versus disorganized search patterns were compared with a Fischer Exact test. The alpha-level that was used to determine significance was $p = .05$ (two-tailed).

We used hypothesis-free VLSM to determine the relationship between the intersections rate and the presence of a lesion in a given voxel [41]. VLSM was performed using Non-parametric Mapping [40]; settings: *t*-test, univariate analysis, only including voxels that were damaged in at least four patients, before and after adjusting for total infarct volume. Correction for multiple testing was performed using an false discovery rate threshold (FDR) with $q < .01$ before, and $q < .05$ after adjusting for total infarct volume, because adjustment for total infarct volume decreases statistical power [5].

We chose to use the continuous intersections rate as outcome measure for our main analysis rather than dichotomized performance, because dichotomization tends to reduce statistical power and does not take into account the degree of disorganization of visual search. To assess the robustness of our results, we additionally performed a qualitative lesion subtraction analysis and repeated the VLSM analysis using the norm-based dichotomized performance on the shape cancellation task as outcome measure; settings: Liebermeister statistic, FDR $q < .05$ [42].

Next, we complemented the VLSM analysis with ROI-based linear regression models, to quantify the impact of region lesion volumes on the intersections rate. For this purpose, 96 cortical and 21 subcortical non-overlapping regions were extracted from the probabilistic Harvard-Oxford atlas (threshold at .25; [16]). Regions for subdivisions of gyri were merged into a single variable, thereby reducing the total number of regions to 89 (e.g., the anterior and posterior division of the inferior temporal gyrus were merged into a single region). Additionally, regions for 16 white matter tracts were extracted from the probabilistic Johns Hopkins University White Matter Tractography Atlas (threshold at .25 [22]) (this atlas contains a total of 20 regions of which only the regions for the superior longitudinal fasciculus (SLF) were not included for this study). Regions for the three branches of the SLF (I–III) were extracted from a previously described subcortical atlas in order to study the impact of infarcts in this tract for each branch separately [38]. All regions were projected on the VLSM results and the amount of voxels with a statistically significant correlation within each region was quantitatively assessed. Regions that appeared to be involved in the intersections rate based on the VLSM results (operationally defined as at least 5% of tested voxels having a statistically significant association between the presence of a lesion and intersections rate, with a total of no less than 100 significant voxels, similar to Refs. [3,5] were selected as ROIs for the linear regression analyses. For every patient, the infarct volumes within these ROIs were computed and entered as independent variables in a linear regression model with the *z*-score of intersections rate as dependent variable, before and after adding total infarct volume to the model.

Finally, an additional sensitivity analysis was conducted, in which the VLSM and ROI-based analyses were restricted to patients with ischemic stroke.

3. Results

A total of 79 patients met our inclusion criteria. One patient had an intersections rate of six standard deviations above the mean of all patients, and was considered an outlier. This patient was excluded from all analyses.

Of the 78 remaining stroke patients, five patients suffered from delayed cerebral ischemia after subarachnoid haemorrhage and 73 patients from ischemic stroke. Clinical characteristics of the patients are provided in Table 1. A disorganized visual search pattern was found in 21.52% of patients. The *z*-scores of intersections rate ranged from −0.94 to 0.57 with a median of −0.60 in the organized search group, and from 0.90 to 3.77 with a median of 1.47 in the disorganized search group.

There were no significant differences between patients showing an organized search pattern versus patients showing a disorganized search pattern regarding gender, age, time post-stroke, MMSE, Barthel Index, Motricity Index arm, Motricity Index leg, or SAN score (all $p > .064$).

The lesion locations in the organized and disorganized search groups are shown in Table 2. Of patients with disorganized visual

Table 1
Mean scores of clinical characteristics and intersections rate in relation to search organization.

	N	Organized search (SD)	*N*	Disorganized search (SD)	Statistics
Gender (% male)	62	62.9%	16	62.5%	$\chi^2(1, N=78) = .001$, $p = .976$
Age (years)	62	57.11 (11.10)	16	55.38 (16.50)	$U = 494.5$; $Z = -.02$; $p = .985$
Time post-stroke (days)	62	32.02 (24.25)	16	43.75 (39.0)	$U = 416.0$; $Z = -.99$; $p = .322$
MMSE (0–30)	44	26.82 (2.90)	12	25.33 (4.70)	$U = 226.5$; $Z = -.76$; $p = .448$
Barthel index (0–20)	54	13.22 (5.84)	12	9.92 (5.30)	$U = 213.0$; $Z = -1.85$; $p = .064$
Motricity index arm (0–100)	53	65.74 (39.20)	12	54.42 (38.32)	$U = 259.0$; $Z = -1.03$; $p = .064$
Motricity index leg (0–100)	52	73.02 (35.94)	12	63.42 (38.32)	$U = 252.5$; $Z = -1.07$ $p = .286$
SAN (0–7)	56	5.54 (1.86)	12	5.83 (1.53)	$U = 321.0$; $Z = -.25$; $p = .799$
Intersections rate (0–1)	62	.056 (.048)	16	.288 (.087)	$U = .000$; $Z = -6.15$; $p < .001$*

MMSE: Mini-Mental State Examination; SAN: Stichting Afasie Nederland.
* Statistically significant with an alpha-level of $p < .05$.

Table 2
Location of ischemic lesion in relation to search organization.

	Organized search ($n = 62$)	Disorganized search ($n = 16$)
Left hemisphere	26 (41.94%)	2 (12.50%)
Right hemisphere	22 (35.48%)	12 (75.0%)
Infratentorial	7 (11.29%)	0 (0%)
Multiple locations	7 (11.29%)	2 (12.60%)

search patterns, 75% had a lesion in the right hemisphere compared to 35% of patients with organized search patterns ($p = .023$).[1]

3.1. Voxel-based lesion-symptom mapping

The spatial distribution of infarcts and the voxels that were damaged in at least four patients are depicted in Fig. 2A . The VLSM analysis identified a substantial number of right hemispheric voxels with a statistically significant association between the presence of a lesion and higher intersections rate (i.e., disorganized search), mostly located in right parietal, occipital and temporal cortices (Fig. 2B). The exact location of these significant voxels is provided in Table 3. Several voxels remained significant after correction for total infarct volume, which were located in the right lateral occipital cortex, superior parietal lobule and postcentral gyrus, and, within the white matter, the right inferior longitudinal fasciculus (ILF), the first branch of the right superior longitudinal fasciculus (SLF I), and the right inferior fronto-occipital fasciculus (IFO) (Fig. 2C).

The lesion overlay and subtraction plots of patients with a disorganized and organized search pattern are shown in Fig. 3A–C. When the VLSM analysis was repeated using norm-based dichotomized performance (disorganized versus organized search) as the dependent variable instead of the intersections rate, the results were essentially the same: lesions in right parietal, occipital and temporal regions were again associated with disorganized search (Fig. 3D).

3.2. Region of interest-based analyses

In total, 16 right hemispheric regions were selected as ROIs, based on the VLSM results (listed in Table 3). In the linear regression model with *z*-scores for intersections rate as the dependent variable, we first added age and sex, which explained only 1.3% in variance and was not significant ($p = .617$). Subsequently, total infarct volume was added, which explained an additional 10.2% in variance ($p = .005$). Finally, infarct volumes within the 23 ROIs were added to the model (Table 4). Infarct volumes within the right middle and superior temporal gyrus, lateral occipital cortex, superior parietal lobule, supramarginal gyrus, ILF, SLF I, and IFO were correlated with intersections rate, independent of total infarct volume. The increase in explained variance on top of age, sex and total infarct volume was highest for infarct volume within the right SLF I (increase in explained variance of 13.8%; $p = .001$). The results of the linear regression analyses without correction for total infarct volume are reported in Supplementary Table 1.

Finally, in the sensitivity analyses in which the VLSM and ROI-based analyses were restricted to patients with ischemic stroke, the results were essentially the same (Supplementary Fig. 2 and Table 2).

4. Discussion

In this study, we aimed to find the anatomical correlates of visual search organization by using a computerized version of a cancellation task and applying lesion-symptom mapping in a sample of 78 stroke patients. The intersections rate, based on the amount of path crossings between consecutive cancelled shapes, was used as a measure for visual search organization [14,37,47]. We found a clear dominance for the right hemisphere in search organization. The grey matter regions that were related to disorganized search during cancellation were located within the parietal lobe (i.e., the right postcentral gyrus, superior parietal lobule and the supramarginal gyrus), within the temporal lobe (i.e., the right superior and middle temporal gyri), and within the occipital lobe (i.e., the right lateral occipital cortex). The white matter tracts that were associated with search organization were the right inferior longitudinal fasciculus (ILF), the first branch of the right superior longitudinal fasciculus (SLF I), and the right inferior fronto-occipital fasciculus (IFO).

The contribution of these different areas is informative with regards to the various components underlying visual search organization. We found that lesions in the posterior part of the right cortex (parietal, occipital and temporal areas) were associated with disorganized search. These results are reminiscent of findings with patients with posterior cortical atrophy (PCA), a neurodegenerative condition. In PCA, patients show reductions of grey matter in regions of the occipital and parietal lobes followed by areas in the temporal lobe [13], with an asymmetry between hemispheres (greater reductions right than left). PCA patients show visuospatial and visuoperceptual impairments, deficits in working memory and features of Bálint's syndrome (including simultanagnosia, oculomotor apraxia, optic ataxia, environmental agnosia [13], disorganized ocular exploration, and revisiting behaviour [35]). The overlap in associated brain areas indicates that these functions might be involved in the organization of search.

Some of the specific brain areas that were associated with disorganized search in the current study have previously been related to spatial remapping and spatial working memory [34]. For instance, lesions within the right inferior parietal lobule [6] and the right

[1] The two patients in the disorganized search group who had an isolated lesion in the left hemisphere were both right handed. Lesions were located both cortical and subcortical: frontoparietal in the first patient, and frontal, parietal and temporal in the second patient.

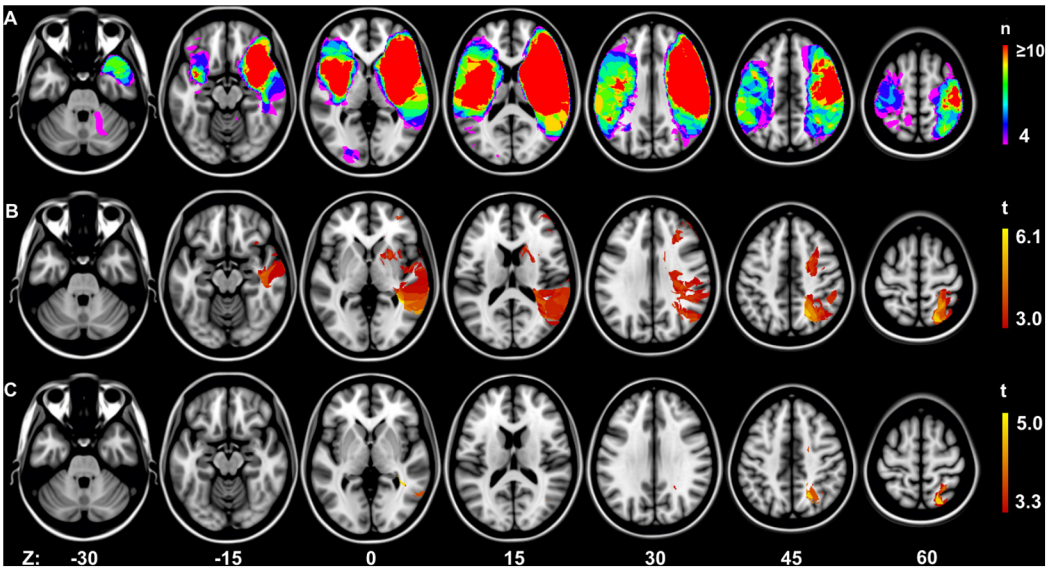

Fig. 2. Distribution of ischemic lesions and VLSM results. The results are projected on the MNI-152 template. The right hemisphere is depicted on the right. (A) Voxels that are damaged in at least four patients are plotted. The coloured bar indicates the number of patients with a lesion for a given voxel. (B) Map of the voxelwise association (t-statistic) between the presence of a lesion and the intersections rate. Voxels exceeding the FDR threshold ($q = .01$) are rendered on a scale from red to yellow. (C) Map of the voxelwise association (t-statistic) between the presence of a lesion and the intersections rate, adjusted for total infarct volume. Voxels exceeding the FDR threshold ($q = .05$) are rendered on a scale from red to yellow. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Voxel-based lesion-symptom mapping results for intersections rate: tested and significant voxels for each ROI.

Anatomical regions	Patients with lesion (n)[a]	Region size in voxels (n)	Tested voxels (n)	Significant voxels before correction for total infarct volume (n [%])	Significant voxels after correction for total infarct volume (n [%])
Grey matter					
R superior temporal gyrus	22	5509	5500	3697 (67.22%)	0
R middle temporal gyrus	16	20577	11690	7150 (61.16%)	0
R superior parietal lobule	19	11800	8635	4843 (55.98%)	28 (0.32%)
R lateral occipital cortex	22	54872	21936	11630 (53.02%)	796 (3.63%)
R heschl's gyrus	26	2223	2223	974 (43.81%)	0
R angular gyrus	17	11704	11657	4879 (41.85%)	0
R supramarginal gyrus	25	16304	16300	6572 (40.32%)	0
R planum Temporale	22	3538	3538	1396 (38.69%)	0
R planum polare	24	2998	2998	519 (17.31%)	0
R caudate	27	4165	4041	643 (15.91%)	0
R parietal operculum cortex	23	4290	4290	549 (12.80%)	0
R frontal pole	24	65201	26520	3131 (11.81%)	0
R postcentral gyrus	26	25920	18473	1508 (8.16%)	6 (0.03%)
R insular cortex	29	10801	10801	804 (7.44%)	0
R pallidum	24	2147	2143	154 (7.19%)	0
R middle frontal gyrus	25	22069	21289	1270 (5.97%)	0
White matter					
R ILF	23	4486	2255	1367 (60.62%)	45 (2%)
R SLF I	12	2301	559	207 (37.03%)	33 (5.90%)
R SLF II	25	1930	1930	179 (9.27%)	0
R SLF III	29	5185	5185	945 (18.23%)	0
R IFO	31	7880	5643	1397 (24.76%)	151 (2.68%)
R ATR	31	8153	4948	913 (18.45%)	0
R CST	28	5021	3169	439 (13.85%)	0

ATR: anterior thalamic radiation; CST: corticospinal tract; IFO: inferior fronto-occipital fasciculus; ILF: inferior longitudinal fasciculus; R: right; SLF: superior longitudinal fasciculus. Regions for which our criterion for involvement was met (i.e., 5% of tested voxels had a statistically significant association between the presence of a lesion and intersections rate, with a minimum of 100 significant voxels) are shown here; the remaining regions are not shown.

[a] Indicates how many of the 78 patients had a lesion (≥1 voxel) within the specified region.

parietal and insula regions [30] are related to impaired performance in spatial working memory tasks. Furthermore, the superior and inferior parietal lobule were related to sustained attention to spatial locations [29]. Spatial working memory and sustained attention are important in both conjunctive search tasks and cancellation tasks: previously searched locations have to be memorized throughout the trial, and the visual representation of the world must be updated, in order to prevent searching the same location repeatedly and to search all locations within the stimulus field. In conjunctive search, participants have to find a target which cannot be distinguished from distractors on the basis of a single feature [50]. Not surprisingly, in a recent study, lesions in similar brain areas as those that were found in the current study were associated with poor conjunctive search: occipital (middle occipital gyrus), posterior parietal (angular gyrus), and temporal cortices (superior and middle temporal gyri extending to the insula), and white matter

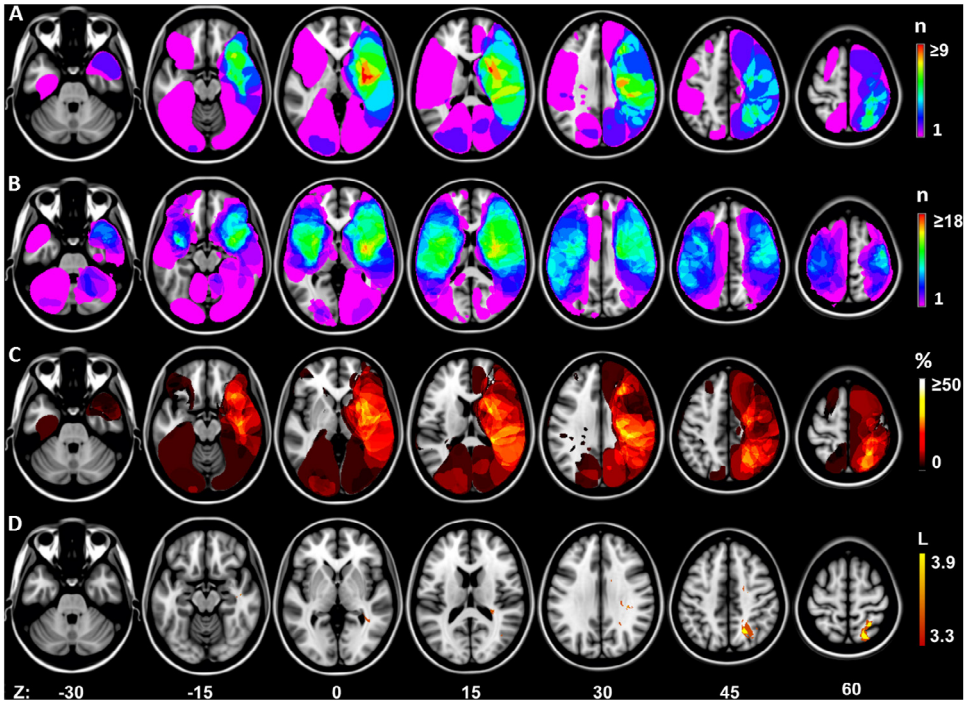

Fig. 3. Lesion overlay and subtraction plots, and VLSM results with dichotomized performance as outcome. The results are projected on the MNI-152 template. The right hemisphere is depicted on the right. The overlay plots show the number of patients with a lesion for a given voxel separately for patients who showed a disorganized (A) and an organized (B) visual search pattern. (C) The lesion subtraction plot depicts which voxels are more frequently affected in patients who showed a disorganized search pattern compared to patients who showed an organized search pattern. (D) Map of the voxel wise Liebermeister statistic with norm-based dichotomized performance (i.e., disorganized versus organized search). Voxels that were damaged significantly more often in patients who showed a disorganized search pattern are rendered on a scale from red to yellow (corrected for multiple testing with FDR $q = .05$).

Table 4
Results of linear regression models with intersections rate as outcome after correction for total infarct volume.

Model	Independent variables	R^2	$p\Delta R^2$	B (95% CI)
1	Age, sex	.013	.617	
2	Model 1 + total infarct volume	.115	.005*	.003 (.001 to .006)
2a	Model 2 + R superior temporal gyrus	.167	.036*	.024 (.014 to .394)
2b	Model 2 + R middle temporal gyrus	.169	.033*	.093 (.008 to .178)
2c	Model 2 + R superior parietal lobule	.222	.002*	.179 (.066 to .292)
2d	Model 2 + R lateral occipital cortex	.212	.004*	.050 (.017 to .083)
2e	Model 2 + R heschl's gyrus	.159	.055	.341 (−.008 to .689)
2f	Model 2 + R angular gyrus	.160	.054	.086 (−.001 to .172)
2g	Model 2 + R supramarginal gyrus	.161	.049*	.067 (.000 to .134)
2h	Model 2 + R planum Temporale	.153	.074	.221 (−.022 to .463)
2i	Model 2 + R planum polare	.137	.183	.201 (−.097 to .500)
2j	Model 2 + R caudate	.135	.200	.150 (−.081 to .382)
2k	Model 2 + R parietal operculum cortex	.144	.125	.145 (−.041 to .331)
2l	Model 2 + R frontal pole	.123	.411	.018 (−.025 to .060)
2m	Model 2 + R postcentral gyrus	.123	.433	.023 (−.035 to .081)
2n	Model 2 + R insular cortex	.135	.202	.043 (−.023 to .109)
2o	Model 2 + R pallidum	.133	.225	.235 (−.148 to .619)
2p	Model 2 + R middle frontal gyrus	.117	.750	.009 (−.046 to .064)
2q	Model 2 + R ILF	.179	.020*	.450 (.072 to .827)
2r	Model 2 + R SLF I	.253	.001*	1.744 (.714 to 2.773)
2s	Model 2 + R SLF II	.126	.358	.277 (−.321 to .875)
2t	Model 2 + R SLF III	.138	.165	.118 (−.050 to .286)
2u	Model 2 + R IFO	.167	.037*	.186 (.012 to .359)
2v	Model 2 + R ATR	.140	.151	.146 (−.054 to .347)
2w	Model 2 + R CST	.133	.229	.209 (−.135 to .554)

ATR: anterior thalamic radiation; CST: corticospinal tract; IFO: inferior fronto-occipital fasciculus; ILF: inferior longitudinal fasciculus; R: right; SLF: superior longitudinal fasciculus. The explained variance (R^2) in intersections rate is given for each model with the corresponding p-value for the difference in explained variance (ΔR^2) between the model and the previous model. The unstandardized coefficient (B) applies to the change in z-score of intersections rate for every 1 ml increase in infarct volume with higher z-score meaning more disorganized search.

* Statistically significant with an alpha-level of $p < .05$.

damage within pathways including the IFO, the internal capsule and the SLF [23]. A lesion in the IFO also correlated with intersections rate in the current study. The association of the IFO with disorganized search and conjunctive search may be explained by the fact that this white matter tract is important in peripheral vision and processing of visual spatial information [32,44]. The IFO connects the frontal lobe with the postero-lateral temporal, parietal and occipital lobes, including the superior parietal lobule, which was associated with search organization in the present study.

The most obvious finding to emerge from our analyses is that of all patients who showed a disorganized search pattern, 75% had an unilateral lesion in the right hemisphere. In prior research, right hemispheric dominance was found for spatial working memory and spatial remapping [34], as well as for the related attentional disorder visuo-spatial neglect [15,24,33]. To summarize, it is likely that deficits in spatial working memory and sustained attention to spatial locations contribute to disorganized visual search.

Another important finding was that infarcts in the superior temporal gyrus correlated with intersections rate. Danckert and Ferber [15] speculated that the superior temporal gyrus might be important for integrating different faculties (e.g., encoding locations and identities of objects, spatial working memory, reorienting attention) into a coherent whole, which is necessary in order to perceive a stable environment and search according to an organized pattern. This speculation was based on several findings. First, the superior temporal gyrus is thought to be involved in reorienting of attention, as patients with lesions at this site have longer RTs to contralesional targets following ipsilesional cues [15,19]. Additionally, the superior temporal gyrus is involved in encoding the locations and identities of objects, which was found by measuring regional cerebral blood flow while subjects engaged in retrieval or perceptual matching of spatial location and object identity [15,26]. Finally, neurophysiological recordings have learned that polysensory neurons, found in the superior temporal sulcus, are multimodal, they have large receptive fields, and receive input from both the dorsal and ventral stream.

In the current study it was also shown that lesions in the SLF I and in the right temporoparietal junction (TPJ; involving the right middle and superior temporal gyrus and right supramarginal gyrus) correlated with intersections rate. Given the known role of these areas in the dorsal and ventral attentional systems, this may indicate that an impairment in search organization is related to a damaged ventral and/or dorsal attentional system, or to a lack of proper communication. On the one hand, the dorsal network is involved in top-down attention (i.e., the voluntary deployment of attention), and contains the intraparietal sulcus and the frontal eye fields of each hemisphere. The SLF I is known to connect dorsal frontoparietal areas: this white matter tract connects the posterior supramarginal gyrus and the posterior portion of the superior temporal gyrus [32], brain areas that were both associated with search organization in the current study. Additionally, the SLF I is connected to the inferior parietal lobule.

On the other hand, the ventral network is involved in bottom-up attention (i.e., the reorientation to unexpected events), and contains the TPJ and the ventral frontal cortex [15,52]. Whereas the SLF III connects ventral frontoparietal areas [48], the SLF II is known to connect the dorsal and ventral networks, and may act as a modulator for the dorsal network [48]. Although a lesion in the SLF II is a predictor of neglect [49], damage to the SLF II and SLF III was not related to disorganized search. It is possible, however, that damage in one system could affect the functionality in structurally intact remote networks [52]. For example, prior research in stroke patients showed that structural damage of ventral areas was accompanied by a functional impairment in the dorsal network [52]. It is possible, therefore, that disorganized search could result from both impairments in the ventral and dorsal attentional system, as flexible interaction between the two systems is necessary for the dynamic control of attention [52].

The final white matter tract that was related to search organization, was the ILF. The ILF connects the anterior part of the temporal lobe to the occipital lobe [32]. The direct pathway of the ILF connects with the superior and middle temporal gyri, which were also associated with organized search. Furthermore, the inferior temporal gyrus, fusiform gyrus, parahippocampal gyrus, amygdala, and hippocampus are connected with the ILF. Among other functions, the ILF has been implicated in face recognition, visual perception, reading and language [32]. However, the exact role of the ILF remains unclear.

The anatomy of neglect matches the TPJ-ventral frontal cortex system [12,15,24,33]. Neglect is thought to result from interacting impairments, including biases in attentional orienting and exploratory motor behaviours, deficits in spatial remapping and a deficit of spatial working memory [15]. All these impairments contribute to neglect, but it is currently unknown whether these distinct types of impairment always co-occur in neglect [15,36]. The overlap between the brain areas related to neglect and disorganized search are in line with prior research, which showed that neglect is a marker for disorganized search [31,37,47]. These studies have used the difference in number of omissions between left and right on a shape cancellation task as a measure of neglect and related this difference to the intersections rate. In the study of [31] only patients with left-sided neglect were included. Ten Brink et al. [47] found that both left and right brain damaged patients with neglect searched less organized than stroke patients without neglect. However, search was least organized in right brain damaged patients, either with or without neglect. To conclude, despite the close relationship, disorganized visual search and neglect seem to be distinct phenomena which can occur independently of each other [31,47].

In prior research, planning and executing an organized search pattern has been linked to executive function. Search cancellation outcome measures, including the amount of intersections, are even called “executive organization measures on cancellation” [31,54]. This link seems plausible in the sense that spatial working memory and sustained attention, which are relevant for organized search, are sometimes considered aspects of executive function [2]. Executive function is highly associated with the frontal lobes [2,21], but in the current study no relation was found between frontal lesions and disorganized visual search during cancellation. Furthermore, the right hemispheric dominance indicates spatial working memory and attentional deficits rather than an executive disorder. Possibly, this could be explained by the simplicity of cancellation tasks. No complex higher order cognitive flexibility, social tact, or problem-solving are required, which are more typical components of executive functioning [2,21]. During cancellation tasks, the ‘plan’ that has to be executed is straightforward, and several strategies (e.g., following a specific pattern or cancelling targets that are in close proximity of each other) could result in an organized search pattern [47].

In the current study, both patients with ischemic stroke and delayed cerebral ischemia after subarachnoid haemorrhage were included. It is thought that subarachnoid haemorrhage can affect brain function both at a macroscopic and microscopic, synaptic level [1]. These microscopic changes might be functionally relevant but could not be taken into account in our analyses. However, the reproduction of our main findings in the sensitivity analyses in which only patients with ischemic stroke were included indicates that this has not affected our results.

Furthermore, hemianopic patients were not excluded. It could be argued that visual search disorders simply result from hemianopic field loss. We consider this unlikely, however, since visual search is more severely affected in hemianopic patients with right brain damaged compared to hemianopic patients with left brain

damage, which supports the idea a visual field deficit alone cannot account for disturbed visual search [28,55].

4.1. Limitations

A limitation of the current study is that VLSM can only be applied to voxels that are damaged in a certain amount of patients. As a consequence, we cannot draw any conclusions regarding regions that were affected in less than four patients.

Furthermore, VLSM constitutes a region-based approach to determining the anatomical correlates of a given function, as opposed to a network-based approach. In other words, VLSM does not take into account the possibility that a lesion at a given location may cause dysfunction in other nodes of a functional brain network, impairing processes other than those mediated by neurons at the lesion location (the distributed injury hypothesis [10]). For example, it is now known that many fibre pathways connect cortical areas that are relevant for spatial orienting and exploration [46] and it has been argued that disorders such as neglect are better explained by dysfunctional cortical networks than by lesions of specific brain regions [11,45]. We therefore included ROIs for major fibre pathways in our region of interest-based analyses.

5. Conclusions

This study has shown that post-stroke disorganized visual search during cancellation tasks is most strongly related to the right hemisphere, in particular the temporoparietal junction (TPJ). These correlates overlap with regions that have previously been associated with conjunctive search, spatial remapping and working memory, the ventral and dorsal attentional systems and visuospatial neglect. This suggests that disorganized visual search during cancellation tasks is caused by disturbed spatial processes, rather than complex higher order executive function or planning, which is more related to frontal regions.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbr.2016.02.004.

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