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Rightward bias in right hemisphere infarct patients with or without thrombolytic treatment and in healthy controls

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Right hemisphere (RH) infarct patients have a tendency to begin visual scanning from the right side of a given stimulus. Our aim was to find out whether RH patients with (T+) or without (T−) thrombolytic treatment and healthy controls differ in their starting points in three cancellation tasks. Our sample comprised of 77 patients and 62 controls. Thirty-four patients received thrombolysis. Rightward orientation bias was more evident in the T− group than in the T+ group. The T+ group showed a robust tendency to start all cancellation tasks more often on the right side than the controls. Regardless of whether they had visual neglect, patients in the T+ group showed still defective rightward orienting, possibly indicating residual attentional problems. The analyses of starting points in visual cancellation tasks provide additional information on residual symptoms of attention difficulties after stroke.

Keywords: Attention; Cognition; Neglect; Rightward bias; Stroke; Thrombolysis.

Cognitive disorders occur frequently in the first weeks after stroke (Nys, van Zandvoort, de Kort, Jansen, de Haan, & Kappelle, 2007). One of the most common and disabling consequences of right hemisphere (RH) stroke is left visual neglect (Bowen, McKenna, & Tallis, 1999; Jehkonen et al., 2000). Reported prevalence of visual neglect vary widely, depending on such factors as the patient population surveyed, the timing of the assessments after stroke, and the choice of clinical tasks used to detect neglect (Azouvi et al., 2002; Bowen et al., 1999; Jehkonen, Laihosalo, & Kettunen, 2006).

Previous experimental studies (Bartolomeo, 1997, 2000; Samuelsson, Hjelmqvist, Jensen, Ekholm, & Blomstrand, 1998) have found that RH patients with or without visual neglect show pathological attention processes (slower reaction times to left-sided than to right-sided stimuli) at the acute phase and at 6–7 months post-stroke. This rightward tendency is strongest in patients

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with visual neglect, but it is also evident in patients with milder attention deficits (Gainotti, D'Erme, & Bartolomeo, 1991) and in RH patients who have recovered from left neglect (Mattingley, Bradshaw, Bradshaw, & Nettleton, 1994). Assessments of visual neglect based on cancellation tasks have found that from a clinical point of view, the most sensitive measure is not the number of omissions, but the spatial location of the starting point spontaneously used by the patient (Azouvi et al., 2006). Apparently recovered RH neglect patients (no left-sided omissions in cancellation tasks) may demonstrate signs of spatial bias when confronted with a novel situation (Webster et al., 1994).

Between 50 and 70% of RH patients without visual neglect showed rightward orienting in widely used paper-and-pencil tasks (Azouvi et al., 2006; Jalas, Lindell, Brunila, Tenovuo, & Hämäläinen, 2002; Potter, Deighton, Mehool, Fairhurst, & Donnelly, 2000). The frequency of starting on the right side was dependent on the type of task (Jalas et al., 2002; Samuelsson, Hjelmqvist, Naver, & Blomstrand, 1996), but patients with left visual neglect (number of left-sided omissions) showed a tendency of rightward orienting regardless of the nature of the task (Jalas et al., 2002). Patients with visual neglect started on the right side almost without exception (Jalas et al., 2002; Nurmi et al., 2010).

Several studies have shown that patients who receive thrombolytic treatment within the first 3 hours of ischemic stroke can expect a favorable 3-month clinical outcome (Hacke et al., 1998; Lindsberg et al., 2003; Merino et al., 2007). However, the effect of thrombolysis on visual attention in the acute stage of stroke has so far received only limited attention. In the study of Laihosalo et al. (forthcoming) 28 RH patients treated and 28 non-treated patients with thrombolysis were evaluated at the acute phase of RH stroke. The results suggest that thrombolytic treatment is related to a favorable effect on visuoperceptual functions in acute phase of stroke (Laihosalo et al., forthcoming). Nys et al. (2006) have suggested that thrombolytic treatment after RH infarct is associated with a favorable outcome in activities of daily living, but not in different cognitive functions during a 6–10-month follow-up.

The association between thrombolytic treatment and visual attention, particularly rightward orientation bias, following acute RH brain infarct has previously not been systematically studied. This study was designed to examine the starting points (left or right) of RH patients with (T+) or without (T−) thrombolytic treatment, and secondly to compare the results of the T+ group and healthy controls.

PATIENTS AND METHODS

Patients

We screened 1458 consecutive patients for inclusion in this study. They were admitted to a university hospital as emergency cases between June 2005 and June 2008. Patients were excluded based on the following criteria: LH stroke ($n = 276$), transient ischemic attack ($n = 200$), previous stroke ($n = 185$), age over 80 years ($n = 144$), cerebral hemorrhage ($n = 139$), other neurological diagnosis ($n = 137$), unable to participate in neuropsychological examination ($n = 95$ patients), significant findings in CT not related to acute stroke ($n = 92$), brain stem or cerebellar stroke ($n = 57$), right hemisphere infarct without thrombolytic treatment ($n = 43$), psychiatric disorder ($n = 20$), substance abuse ($n = 21$), traumatic brain injury ($n = 6$), left-handedness ($n = 5$), and native language other than Finnish ($n = 4$). All the patients included in the sample were native Finns nationals and they were studied in their mother tongue. We recorded the patient's age, gender, and educational level.

Thrombolytic treatment was administered within the first 3 hours of stroke as recommended in the National Institute of Neurological Disorders and Stroke study (NINDS) (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995). Exclusion criteria for thrombolytic treatment were adopted from the NINDS (1995) (e.g., RH patients did not receive thrombolysis if time of stroke onset was more than 3 hours or was not exactly known) with the following additional exclusion criteria: patients with infracted area involvement of more than one third of the middle cerebral artery territory on the baseline computed tomography (CT) scan were excluded because they were possibly at higher risk of hemorrhage and less likely to benefit from thrombolytic treatment (Von Kummer, Allen, Holle, Bozzao et al., 1997). Treatment decisions were made by experienced neurologists.

The study protocol was approved by the Ethical Committee of the Hospital District. Informed consent was obtained from all the participating patients before inclusion in the study.

Neuropsychological and neurological examination

A neuropsychological examination was conducted at a mean of 4.0 ± 2.2 days after stroke onset (range = 1–11 days). Presence of visual neglect was evaluated with the six conventional paper-and-pencil subtests of the Behavioural Inattention Test (BITC) (Wilson, Cockburn, & Halligan, 1987; Jehkonen, 2002). Patients who scored at or below the cut-off point (≤129) for the total BITC score or below the cut-off score on at least two of the six conventional BITC subtests (line crossing, star cancellation, letter cancellation, line bisection, representational drawing, figure or shape copying) were considered to have symptoms of visual neglect. For each subtest we used the same cut-off points as Halligan, Marshall, and Wade (1989). The presence of visual neglect was dichotomized as present (1) or absent (0).

For the analysis of starting points we used three BITC cancellation tasks (Wilson et al., 1987): line cancellation, letter cancellation, and star cancellation. Each standard sheet (A4; 21 × 29.5 cm) was placed directly in front of the patient and aligned with his or her midsagittal plane. The patient was not allowed to move the sheet during the task and no time limit was imposed. The examiner marked the patient's starting point in each task. The starting point was designated left or right with respect to the midline of the paper sheet.

In the neurological examination, the severity of stroke was evaluated using the National Institute of Health Stroke Scale (NIHSS) (Goldstein, Bertels, & Davis, 1989). The degree of stroke severity was defined on the basis of the NIHSS sum score (range: 0–34; 0–1 = none or minimal symptoms, 2–8 = mild symptoms, 9–15 = moderate symptoms, ≥16 = severe symptoms). NIHSS was scored pre-treatment (≤3 hours) on arrival at the emergency department (NIHSS at pre-treatment), and later on the neurological ward (NIHSS at ward) on average 4.3 ± 2.4 days (range: 1–10) after onset. The presence of visual field defect was assessed with using standardized neurological confrontation technique as part of the NIHSS and scored as 1 and absence of hemianopia as 0.

Healthy controls

A reference sample of 62 healthy controls was drawn for the neuropsychological examination from local pensioners' clubs and from among the researchers' acquaintances. Before the examinations, the control group was screened using a semi-structured interview for possible history of alcohol abuse and psychiatric, neurological, or cognitive disorders. The exclusion criterion criteria were same as those of the patients'. All the controls underwent a neuropsychological examination following the same protocol as the RH group. All the subjects were Finnish, right-handed, studied in their mother tongue, and were blind to the hypotheses of the study. We recorded the control's age, gender and educational level. Education was dichotomized as low (≤9) or high (≥10 years).

Statistical analyses

Since some of the parameters were not normally distributed and the sample sizes were small, we chose to use non-parametric tests for continuous variables. Group differences in continuous variables (age, years of education, BITC sum score, days from onset to examination, NIHSS) were analyzed using the Mann–Whitney *U*-test. Categorical variables (starting point, gender, level of education, presence of hemianopia, and visual neglect) were compared using cross-tabulations. The level of statistical significance was set at .05 for all analyses. All reported *p*-values are based on two-tailed tests.

RESULTS

In this study, we enrolled 34 RH patients with thrombolytic treatment in the T+ group, 43 RH patients without thrombolytic treatment in the T− group, and 62 healthy controls in the control group. Their median age was 62 years (range: 30–79) and median years of education 10 (range: 6–20). The RH patients' clinical characteristics are shown in Table 1.

Comparison between patients with or without thrombolytic treatment

The groups did not differ significantly with respect to age, gender, years of education, days from onset to neuropsychological or neurological examination, BITC sum score, presence of hemianopia or presence of visual neglect. NIHSS scores at pre-treatment did not differ significantly between two groups, but at ward the T− group had statistically

TABLE 1
Clinical characteristics of patients with (T+) and without (T−) thrombolysis and the comparison between the groups

	T+ (n = 34)	*T− (n = 43)*	*p-Value*
Male/Female	19/15	31/12	.090
Age: Md (range)	60.5 (30–77)	62.0 (36–79)	.252
Education in years: Md (range)	10.0 (6–16)	9.0 (6–20)	.278
NIHSS sum score at pre-treatment: Md (range)	6.0 (1–17)	4.0 (1–15)	.137
Hemianopia present (%)	5 (16)[a]	6 (14)	.841
Days from onset to neurological examination: Md (range)	5.0 (1–10)[b]	3.0 (1–10)[a]	.305
NIHSS sum score at ward: Md (range)	1 (0–17)[a]	3 (0–14)[b]	.009
Hemianopia present (%)	5 (15)[b]	5 (12)[c]	.745
Days from onset to neuropsychological examination: Md (range)	5.0 (1–10)	3.0 (1–11)	.798
BITC sum score at ward: Md (range)	143.5 (38–146)	142 (31–146)	.150
VN present (%)	5 (15)	12 (28)	.168

Md, median; NIHSS, sum score of the National Institute of Health Stroke Scale (range: 0–34; 0 = no defect; 34 = severe stroke); at pre-treatment, outcome on admission in the emergency department; at ward, outcome at neurological ward; BITC, sum score of six conventional subtests of the Behavioural Inattention Test (range 0–146; ≤129 = visual neglect, ≥130 = no visual neglect); VN, visual neglect.
[a]Missing value for patient.
[b]Three patients had missing values.
[c]Four patients had missing values.

significantly higher NIHSS scores than the T+ group. Figure 1 shows clinical outcome scores of the NIHSS at pre-treatment and at neurological ward in the two patient groups.

In all cancellation tasks the T+ group started from the left side more often than the T− group. In the line cancellation task, 69.7% of the T+ patients and 47.6% of the T− patients started from the left; in the letter cancellation task the figures were 87.5% (T+) and 82.1% (T−); and in the star cancellation task 61.8% (T+) and 41.9% (T−), respectively. The difference was statistically significant in the line cancellation task ($p = .05$), and there was also a trend towards significance in the star cancellation task ($p = .08$) (Figure 2).

In the line cancellation task only 9% of all the T− patients with visual neglect had leftward bias; the figures for the letter cancellation and star cancellation tasks were 45 and 9%, respectively. In the line and star cancellation tasks 40% of all the T+ patients with visual neglect patients had leftward bias, and in the letter cancellation task 60%.

Comparison between healthy controls and patients with thrombolytic treatment

In the second analysis, the two groups did not differ significantly in age, gender, level of education, or BITC sum score. In the sample of 34 RH patients with thrombolysis, only five had visual neglect.

The control group showed a clear tendency to start on the left side of a given stimulus sheet (letter cancellation task 100%; star cancellation task:

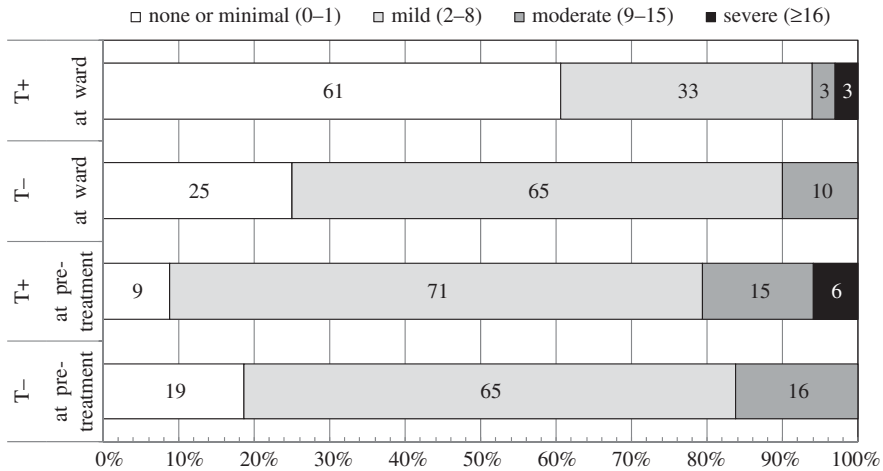

Figure 1. Clinical outcome scores of the NIHSS at pre-treatment and at neurological ward in RH stroke patients with (T+) or without (T−) thrombolytic treatment.

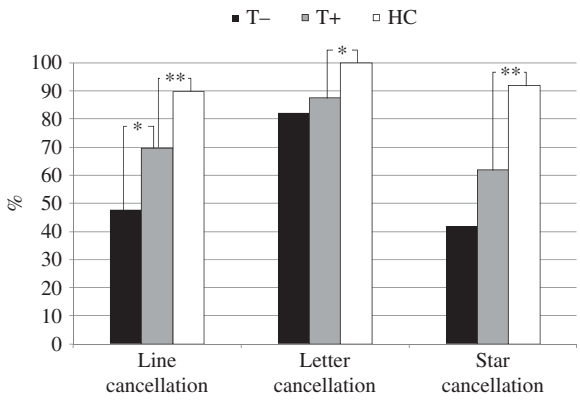

Figure 2. Percentage of left-side starting points in cancellation tasks in thrombolytic (T+) and non-thrombolytic (T−) groups, and in healthy controls (HC). (*Denotes statistical significance at the level of $p < .05$ and $^{**}p < .01$).

91.9%; line cancellation task: 89.8%). The differences in starting points (left vs. right) between the controls and the T+ group were statistically significant in all three cancellation tasks (Table 2). In star cancellation task, 38.2% of the T+ patients started from the right; in line cancellation task 30.3%; and in letter cancellation task 12.1%.

The statistically significant differences in starting points (left vs. right) between the controls and the T+ group with or without visual neglect were found in all three cancellation tasks. Statistically significant differences were found between the T+ patients without visual neglect and controls in line ($p = .040$), letter ($p = .052$) and star cancellation task ($p = .006$). Statistically significant differences were also found between the T+ group with visual neglect and controls in line ($p = .001$), letter ($p < .001$), and star cancellation task ($p = .002$). A statistical difference between the T+ groups with and without visual neglect was observed in letter cancellation task ($p = .041$). Figure 3 illustrates the frequency of left-side starting points in the three cancellation tasks.

DISCUSSION

The purpose of this study was to examine starting points in three cancellation tasks and to compare the results between two homogenous group of RH patients with (T+) or without (T−) thrombolytic treatment and the control group.

Our results suggest that defective rightward orientation bias was more evident in the T− group than in the T+ group. No differences were found between the two groups in presence of visual neglect or stroke severity pre-treatment. Defective right hand start is a common phenomenon in RH patients, and our present findings confirm earlier results (Gainotti et al., 1991; Jalas et al., 2002; Mattingley et al., 1994). This phenomenon is more common and severe in the group with pronounced signs of visual neglect (Webster et al., 1995). Therefore the presence of visual neglect might partly explain why the T− group had more rightward orientation bias than the T+ group (28 vs. 15%). However, we also found some signs that rightward bias was more common in the T− group than in the T+ group regardless of the presence of visual neglect. Our results might indicate that not all RH stroke patients necessarily show recognizable visual neglect in conventional paper-and-pencil tests, but many do show signs of rightward orientation bias, indicating mild or residual inattention.

In the T+ group only five RH patients showed visual neglect, which is far less than previously reported (Bowen et al., 1999; Jehkonen et al., 2000). As expected, the most robust tendency towards

TABLE 2
Participant characteristics in thrombolytic treatment group and in healthy controls and comparison between the groups

	Patients (n = 34)	*Controls (n = 62)*	*p-Value*
Male/Female	19/15	32/30	.690
Age: mean (±SD, range)	60.3 (±11.9, 30–77)	56.2 (±15.2, 30–80)	.273
BITC: mean (±SD, range)	137.8 (±18.8, 38–146)	142.1 (±3.2, 133–146)	.948
Education in years: % (high)	64.7	75.8	.250
Line cancellation: %	30.3[a]	10.2[b]	.015
Letter cancellation: %	12.1[a]	0	.005
Star cancellation: %	38.2	8.1	<.000

SD, standard deviation; BITC, sum score of six conventional Behavioural Inattention Test (range 0–146; ≤129 = visual neglect, ≥130 = no visual neglect); Cancellation, Percentage of right side starting points; High education, duration of education ≥10 years.
[a]Missing value for patient.
[b]Three subjects had missing values.

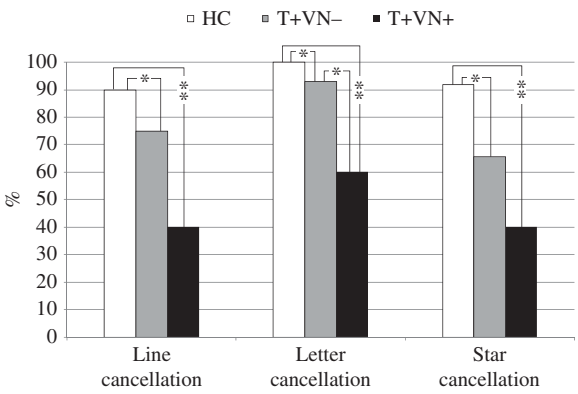

Figure 3. Percentage of left-side starting points in three cancellation tasks in patients with thrombolytic treatment with (T+ VN+) and without visual neglect (T+ VN–), and in healthy controls (HC). (* Denotes statistical significance at the level of $p < .05$ and $^{**}p < .01$).

rightward orienting was found in visual neglect patients; this is in line with previous findings (Azouvi et al., 2006; Gainotti et al., 1991; Jalas et al., 2002; Samuelsson et al., 1996). Statistical differences were found between the T+ group with visual neglect and the T+ group without visual neglect in letter cancellation task, and between the T+ group with visual neglect and the control group in all cancellation tasks. This result might suggest that despite thrombolytic treatment, patients with visual neglect have a robust tendency towards rightward orienting on average 4 days after stroke.

The rightward tendency was apparent regardless of the presence of visual neglect in both groups. Jalas et al. (2002) reported that in the RH group without visual neglect, 43.7% of all search performances were started on the right side of the stimulus array. Our results confirmed the previous finding (Jalas et al., 2002; Samuelsson et al., 1996) that RH patients without visual neglect show a tendency to rightward bias, which might be a sign of a residual automatic orienting problem at the acute phase of stroke.

In keeping with earlier findings (Azouvi et al., 2006; Jalas et al., 2002; Potter et al., 2000), most of the controls in this study tended to start cancellation tasks on the left side of a given stimulus. Only a small proportion of the controls showed rightward bias. Starting on the left was most evident in letter cancellation task showing a ceiling effect. This may be due to the influence of structured stimulus sheet. Randomly arranged stimulus sheet induced more rightward orienting than structured stimulus sheet (Jalas et al., 2002; Samuelsson et al., 1996). Therefore, in letter cancellation task, any deviation from optimal could be considered abnormal.

A comparison of these results for the different groups revealed major differences. The T+ group with and also without visual neglect showed a much stronger tendency to start on the right side than the control group. This is in line with the findings of Jalas et al. (2002), who reported that the difference between RH patients without visual neglect and healthy subjects was statistically significant in cancellation tasks. In our study, this result might suggest that the process of recovery from defective rightward bias after an average of 4 days since stroke onset was incomplete.

A major strength of this study is that it was carried out in a homogeneous group of RH stroke patients who had suffered their first RH infarct. Furthermore, we used standardized paper-and-pencil subtests of the BITC (Halligan et al., 1989) that are in widespread clinical use, and the same cut-off points as Halligan et al. (1989) for each six subtests of BITC. Neuropsychological and neurological evaluations were conducted on average 4 days after stroke onset. One limitation of our study is a quite small number of T+ patients with visual neglect. Furthermore, we only investigated RH stroke patients. This means that the results cannot be generalized to whole stroke population.

In conclusion, the present study suggests that rightward bias was more common in RH patients who did not receive thrombolytic treatment, only a small proportion of our controls were right-biased, and there were indications of task dependent differences in rightward orienting bias. Despite receiving thrombolytic treatment within 3 hours of first-ever RH stroke, patients with or without visual neglect showed an abnormal rightward tendency. Our findings imply a residual pathological attention process, suggesting that spontaneous recovery from abnormal attention is incomplete after on average 4 days. Therefore, future studies should aim to establish spontaneous recovery process of defective rightward bias after a 6-month follow-up.

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