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Thrombolysis and visual neglect after right hemisphere infarct during a 6-month follow-up

Laura Nurmi[a], Eija-Inkeri Ruuskanen[b] and Mervi Jehkonen[a]

[a]Faculty of Social Sciences, Tampere University, Tampere, Finland; [b]Department of Clinical Neurosciences, Turku University Hospital, Turku, Finland

ABSTRACT

We explored the association of thrombolysis with the occurrence of and recovery from visual neglect and associated symptoms, specifically initial ipsilateral orienting bias and slowed processing speed within six months after first-ever right hemisphere infarct. Sixty-two patients, matched for age, years of education and baseline stroke severity, were divided into two groups according whether receiving thrombolysis or not. Visual neglect was assessed with the Behavioral Inattention Test, ipsilateral orienting bias with starting point in cancelation tasks, and processing speed with cancelation time at the acute phase and six months post-stroke. At the acute phase, thrombolytic patients scored significantly better than non-thrombolytic patients with neglect measurements used. The groups did not differ according to starting points or cancelation times. At six months, the groups did not differ according to neglect measurements or starting points. However, thrombolytic patients were significantly faster than non-thrombolytic patients in performing the letter cancelation task. The results indicate association of thrombolysis with less visual neglect symptoms at the acute phase and faster visual search performance at six months. These results support preliminary indications of an association between thrombolysis and favorable short-term cognitive outcomes but also offer first indications of a long-term association between thrombolysis and beneficial cognitive outcome post-stroke.

KEYWORDS

Brain infarct; ipsilateral orienting bias; processing speed; stroke; thrombolytic treatment; visual neglect

Introduction

Visual neglect is a common neuropsychological deficit after right hemisphere (RH) stroke, known to predict poor functional recovery and difficulties in activities of daily living (ADL; Di Monaco et al., 2011; Gammeri et al., 2020; Jehkonen et al., 2006; Nys et al., 2005). The average reported incidence of neglect is 43% for acute RH lesions and 20% for acute left hemisphere lesions (Bowen et al., 1999; Ringman et al., 2004). Patients with neglect fail to report, respond, or orient to contralesional stimuli, without this being caused by primary sensory or motor deficits (Heilman et al., 1993). Rather than a single unitary neuropsychological symptom, neglect is regarded as a syndrome characterized by different lateralized and non-lateralized attentional components that interact with each other (Bartolomeo & Chokron, 2002; Husain & Rorden, 2003; Karnath, 1988; Ricci et al., 2016; Van Vleet & DeGutis, 2013). Besides the deficit in orienting to the contralesional side, another essential symptom is ipsilesional orienting bias, a tendency to initially orient attention to the ipsilesional side of space (Bartolomeo & Chokron, 2002; Gainotti et al., 1991; Karnath, 1988). In left visual neglect this is reflected, for example, in a bias to start visual search in cancelation tasks on the right-hand side, contrary to the typical left-sided start seen in healthy subjects (Azouvi et al., 2006; Nurmi et al., 2010; Samuelsson et al., 1996; Warren et al., 2008). Additionally, slowed processing speed, which is thought to often underlie attentional deficits (Lezak et al., 2012), has been associated with RH lesions in general (e.g. Corbetta & Shulman, 2011; Farnè et al., 2004; Heilman et al., 1993). Furthermore, comparisons of RH patients with and without visual neglect have shown that slow processing speed is even more characteristic of patients with neglect (e.g. Bonato, 2012; Erez et al., 2009; Gerritsen et al., 2003). Slow processing speed has been demonstrated using measures of reaction time and cancelation rate, for example (Bartolomeo & Chokron, 1999; Manly et al., 2009; Robertson & Eglin, 1993; Samuelsson et al., 1998; van Kessel et al., 2010). In some studies, processing has been contralaterally slowed and considered to reflect lateralized deficits (e.g. Behrmann & Meegan, 1998; Smania et al., 1998), while in others slowness has been ipsilateral or bilateral and thought to indicate a deficit in non-lateralized attentional processing instead (e.g. Bartolomeo & Chokron, 2002; Robertson, 1993; van Kessel et al., 2010).

Sometimes RH stroke patients with a preserved ability to orient toward the contralesional side may show ipsilateral orienting bias and/or slowed processing speed, which is considered to indicate milder neglect symptoms without a full-blown neglect syndrome (Gainotti et al., 1991; Nurmi

CONTACT Laura Nurmi laura.nurmi@gmail.com Tampere University, Faculty of Social Sciences, FIN-33014 University of Tampere, Finland.

et al., 2010; 2018; van Kessel et al., 2010). Similarly, as neglect patients are often seen to recover from the most flagrant neglect symptoms (i.e. contralesional orienting deficits) within the first one to three months (Cassidy et al., 1998; Nijboer et al., 2013; Ringman et al., 2004), they may still show ipsilateral orienting bias and/or slowed processing speed as residual neglect symptoms for several months, and up to a year post-stroke (Kettunen, Nurmi, Dastidar, et al., 2012; Mattingley et al., 1994; Nurmi et al., 2018; Samuelsson et al., 1998; Viken, 2013). Thus, when more obvious signs of neglect are absent, ipsilateral orienting bias and slowed processing speed may indicate the presence of mild or residual neglect. When occurring at the acute phase of stroke, ipsilateral orienting bias and slowed processing speed have been found to be important predictors of long-term functional dependency (Viken et al., 2014). Even in the absence of full-blown neglect, these milder symptoms can *per se* cause difficulties in more complex ADL often encountered in real-life situations (Bonato, 2012; Webster et al., 1995).

Thrombolysis with recombinant tissue plasminogen activator (rt-PA), used in treating acute ischemia within 3 to 4.5 hours of stroke onset, has proved significantly beneficial in reducing mortality and functional dependency (Wardlaw et al., 2014). However, research addressing the cognitive outcomes after thrombolysis has still been very limited and methodologically heterogeneous, and the findings somewhat contradictory (Broome et al., 2016). Only few studies have addressed the topic of visual neglect.

A recent retrospective study by Strambo et al. (2020) investigated the outcomes of both thrombolysis and thrombectomy with a focus on cognition in the subacute phase and on disability and visual field defects at three months after ischemic stroke from isolated posterior cerebral artery occlusion. Fifty-one patients had conservative treatment, 34 received thrombolysis and 21 were treated with thrombectomy. Neuropsychological assessment was conducted within one to 10 days from stroke onset and it comprised seven cognitive domains (language, apraxia, visual agnosia, unilateral spatial neglect, long-term memory, executive functions and attention). Neglect was assessed with visual exploration of a picture, line crossing and line bisection. In terms of subacute phase cognition, a trend toward better outcome was found after thrombolysis was compared to conservative treatment, although an even more positive outcome was seen in patients treated with thrombectomy. The three patient groups differed significantly according to apraxia, anterograde memory and executive functions, and with a nonsignificant trend for language and, to a lesser extent, for attention and neglect.

In the study of Nys et al. (2006), the effects of thrombolytic treatment on functional outcome and cognition were examined at six to ten months after ischemic stroke. The study participants comprised 25 thrombolytic patients and 67 non-thrombolytic patients with first-ever ischemic stroke. Functional outcome was examined with basic and instrumental measures of ADL. Neuropsychological assessment included seven cognitive domains (abstract reasoning, verbal and visual memory, executive functioning, visual perception and construction, language and unilateral neglect) and neglect was evaluated using only a star cancelation. Cognitive outcome was then based on a single compound of the seven domains. The treatment was found to have a long-term beneficial association with functional outcome, but not with cognition.

The study of Laihosalo et al. (2011) focused on the association of thrombolysis with visuoperceptual functions in first-ever RH infarct patients. They examined 28 matched thrombolytic and non-thrombolytic pairs. Neuropsychological assessment was conducted on average four days post-stroke and included an evaluation of visuoconstructive abilities, visual search and reasoning, visual memory and visual neglect. Neglect was investigated using the sum score for the six conventional subtests of the Behavioral Inattention Test (BIT; Wilson et al., 1987). Thrombolytic-treated patients showed significantly less acute phase visuoconstructive deficits than non-treated patients, but the groups did not differ according to visual memory and reasoning or visual neglect.

Kettunen, Nurmi, Koivisto, et al. (2012) examined the occurrence of visual neglect at the acute phase of first-ever RH infarct in patients with and without thrombolytic treatment. In addition, they explored whether thrombolysis is a predictor of visual neglect. Out of the 77 patients included in the study, 34 received thrombolysis. Visual neglect was evaluated on average four days post-stroke with the six conventional subtests of the BIT. Again, the thrombolytic and non-thrombolytic groups did not differ significantly according to visual neglect. However, thrombolysis independently predicted absence of visual neglect suggesting that thrombolytic RH infarct patients had a lower risk of acute phase visual neglect compared to conservatively treated patients. In another study, Kettunen, Laihosalo, et al. (2012) investigated the differences in acute phase rightward (here ipsilateral) orienting bias between RH infarct patients with and without thrombolysis and healthy controls. The patient groups were the same as in the former study and the control group consisted of 62 healthy subjects. Rightward orienting bias was evaluated on average four days after infarct onset using the starting points in the three BIT cancelation tasks. The results revealed that thrombolytic RH infarct patients showed rightward orienting bias significantly less than those receiving conservative treatment in the line cancelation task, and a similar trend toward significance was seen in the star cancelation task. However, thrombolytic patients showed significantly more rightward orienting bias than healthy controls in all cancelation tasks.

Indeed, the limited existing literature is somewhat heterogenous in terms of outcome measures, methodologies, patient samples, sample sizes and timing of the assessment. There are some limited and preliminary, albeit somewhat contradictory signs that thrombolysis has an association with favorable short-term cognitive outcomes after an ischemic stroke. The association between thrombolysis and visual neglect, however, is rather unclear. In addition, a little is understood about long-term cognitive outcomes. The aim of this study was to explore whether RH infarct patients with (T+) and without (T-) thrombolytic treatment differ in the occurrence of and recovery from visual neglect during a six-month follow-up. In order to gain increased sensitivity for evaluating the neglect syndrome, we added the measures of cancelation time and starting point to the conventional assessment of neglect, allowing us to additionally examine symptoms often associated with the syndrome, namely initial ipsilateral orienting bias and slowed processing speed.

Methods

Subjects

In total, 2,461 acute stroke patients were consecutively admitted to Tampere University Hospital during two different periods, from June 2005 to July 2008 and from March 2010 to December 2012. Patients who had a neurological diagnosis other than a RH infarct, previous neurological or psychiatric diagnosis, significant cerebral atrophy, significant loss of consciousness, significant loss of primary vision or hearing, substance abuse or whose native language was other than Finnish, who were aged < 30 or > 85 years or unable to live independently prior to infarct, were excluded from this study. As a result, 118 applicable RH infarct patients were diagnosed on the basis of neurological and neuroradiological (Computerized tomography [CT]) examinations on arrival at hospital. Those meeting the criteria for thrombolysis received the treatment within 4.5 hours of infarct onset (T+, n = 67), while others were treated according to a conservative treatment protocol (T-, n = 51) (The National Institute of Neurological Disorders, Stroke rt-PA Stroke Study Group, 1995; Lees et al., 2010). The treatment decision was made by an experienced neurologist. For the patients included in the study, the contraindications for thrombolysis were bleeding risk (e.g. therapeutic anticoagulation), uncontrolled/uncontrollable high blood pressure, too mild or resolving symptoms, time since infarct onset more than 4.5 hours or not exactly known. Conservative treatment refers to stabilizing the patient, e.g. respiratory and cardiac care, management of neurological status, fluid and metabolic balance and vital physiological functions, and prevention/treatment of other possible conditions, e.g. seizures, infections or venous thromboembolism (European Stroke Initiative Executive Committee 2003). For the purposes of this study, the T + and T– patients were matched for stroke severity at the time of arrival at hospital (± 1 point in the National Institution of Health Stroke Scale sum score, NIHSS), age (± 3 years) and years of education (± 2 years) in order to rule out the effects of these factors. With the given criteria, 31 matched pairs could eventually be formed. During the 6-month follow-up, none of the patients had recurrent stroke. Rehabilitation status, i.e. whether a patient received neuropsychological rehabilitation and/or occupational therapy during the six-month follow-up, was gathered from all patients. The study protocol had been approved by the Ethical Committee of Tampere University Hospital, and the human data was obtained in compliance with the Helsinki Declaration.

Methods

Neuropsychological assessment

Neuropsychological assessment was conducted twice, at the acute phase (within seven days of infarct onset) and at six months.

Visual neglect was examined with the six conventional subtests of the BIT (Jehkonen, 2002; Wilson et al., 1987). The neglect criterion was based on failure in at least two subtests, using the cutoff points from Wilson et al. (1987; cutoffs/maximum scores: line cancelation 34/36, letter cancelation 32/40, star cancelation 51/54, figure and shape copying 3/4, line bisection 7/9, representational drawing 2/3; in each task, lower score reflects to more severe neglect symptoms).

Initial ipsilateral orienting bias was evaluated with the starting points for the three BIT cancelation tasks, i.e. the locations from which the cancelation tasks are started (a distance from the sheet's midline in centimeters as negative values for left-sided starting points and positive values for right-sided starting points; possible ranges: line cancelation −13.4 – +13.2 cm; letter cancelation −12.4 – +12.2 cm; star cancelation −11.9 – +14.0 cm). The criterion for ipsilateral orienting bias was an atypical starting point in at least two cancelation tasks, based on guideline values from Nurmi et al. (2010; line cancelation: atypical starting point ≥ −5.8 cm, letter cancelation: atypical starting point ≥ −10.0 cm, star cancelation: atypical starting point ≥ −11).

Processing speed in visual search was examined using the letter and star cancelation tasks by measuring the cancelation time (duration of cancelation performance in seconds) for both tasks separately. These two tasks were chosen because of their relatively higher complexity compared to the line cancelation task, and complex tasks better detect deficits in processing speed than simpler ones (Benton, 1986; Lezak et al., 2012). The criterion for slowed processing speed was a slow cancelation time in at least one of these two tasks, based on the guideline cutoffs from Nurmi et al. (2018; letter cancelation: slow cancelation time ≥ 83 sec, star cancelation: slow cancelation time ≥ 60 sec).

Neurological examination

Neurological examination was carried out three times: on arrival at hospital (baseline), at the acute phase and at six months.

Stroke severity was assessed based on the NIHSS sum score (Goldstein et al., 1989; range 0–34; 0 = no defect, 34 = severe stroke). Hemianopia was examined on a scale from 0 to 2 (0 = no vision loss, 1 = partial hemianopia, 2 = complete hemianopia). Hemiparesis was scored separately for leg and arm on a scale from 0 to 4 (0 = no motor defect, 4 = severe motor defect) and then summed up for a range from 0 to 8. Extinction/inattention was scored on a scale from 0 to 2 (0 = no abnormality, 1 = visual, tactile, auditory, spatial or personal inattention/extinction, profound hemi-inattention/extinction to more than one modality).

Functioning in basic ADL was evaluated using the Barthel Index (BI, Mahoney & Barthel, 1965; range 0–100; 0 = dependent, 100 = independent).

Neuroradiological examination

Neuroradiological examination was conducted twice: after admission to hospital (CT prior to possible thrombolysis) and either at the acute phase or at six months (Magnetic resonance imaging [MRI]).

CT was conducted after admission to hospital according to standard treatment protocol in order to corroborate the infarct diagnosis and to exclude any hemorrhage prior to possible thrombolysis.

MRI examination was used to exclude the presence of significant cerebral atrophy and to locate the infarct by regions of anterior cerebral artery (ACA), medial cerebral artery (MCA) and posterior cerebral artery (PCA).

Data analysis

For statistical analyses of neuropsychological data, we used dichotomic variables of neglect present/not present, ipsilateral orienting bias present/not present and slow processing speed present/not present to offer clinically relevant information about the occurrence of neglect related symptoms in the patient groups of this study. In addition, for more detailed statistical analyses we used the raw scores with following variables: *Visual neglect:* BIT sum score (including six subtests; possible range 0-146), cancelation task sum score (including three cancelation tasks; possible range 0-130), figure and shape copying (possible range 0-4), line bisection (possible range 0-9), representational drawing (possible range 0-3) and number of failed subtests (possible range 0-6); *Ipsilateral orienting bias:* starting point for line cancelation task (possible range: −13.4 – +13.2 cm) and starting point for star cancelation task (possible range: −11.9 – +14.0 cm). Only the starting points for line and star cancelation tasks were included since they are found to be particularly sensitive in detecting ipsilateral orienting bias (Nurmi et al., 2010); *Processing speed:* cancelation time in letter cancelation task and cancelation time in star cancelation task.

Because of the skewed distribution of variables and small sample sizes, nonparametric methods were used for statistical analyses. For continuous variables the comparisons were made using the Wilcoxon test and for categorical/binominal variables using the McNemar test. Effect size was calculated for Wilcoxon analyses by computing η^2 (Fritz et al., 2012). Cohen's guidelines for η^2 were used (Cohen, 1988, as cited in Fritz et al., 2012; a large effect: .14, a medium effect: .06, and a small effect: .01). Statistical analyses were done using the Statistical Package for the Social Sciences version 23 for Windows. *P*-values less than .05 were defined as statistically significant.

Results

Demographic and clinical characteristics

The demographic and clinical characteristics of the T + and T− groups are presented in Table 1. On arrival at hospital, the T + group had significantly more severe motor defect (baseline hemiparesis) than the T− group. At the acute phase, the T− group had significantly more severe stroke (NIHSS sum score) than the T + group. The two groups did not differ significantly on any other demographic or clinical characteristics at any point of measurement. In both groups the most typical infarct location was in the region of the middle cerebral artery (MCA).

Table 1. Demographic and clinical characteristics and comparisons of patients with (T+) and without thrombolytic treatment (T−) matched by age, education and baseline stroke severity (NIHSS).

Variable	T− n = 31	T+ n = 31	Wilcoxon Z	*p*-value
Male/Female	25/6	20/11	(McNemar)	.180
Age: Md (range)	66 (44–79)	66 (47–81)	−.537	.591
Education in years: Md (range)	9 (6–16)	9 (6–16)	−1.309	.191
Baseline NIHSS: Md (range)	5 (1–13)	5 (1–14)	−.229	.819
Baseline hemianopia: present (%)	6 (19%)	5 (16%)	−1.127	.260
Baseline hemiparesis: Md (range)	1 (0–6)	2 (0–8)	−2.050	**.040**
Baseline extinction/inattention: Md (range)	0 (0–2)	0 (0–2)	−1.342	.180
Days to acute phase examination: Md (range)	3 (1–6)	4 (2–7)	−.575	.565
NIHSS at acute phase: Md (range)	2 (0–8)[a]	0 (0–19)	−2.130	**.033**
Hemianopia at acute phase: present (%)	4 (13%)	3 (10%)	−.966	.334
Hemiparesis at acute phase: Md (range)	0 (0–5)	0 (0–8)	−.441	.659
Extinction/inattention at acute phase: Md (range)	0 (0–2)[a]	0 (0–1)	−.812	.417
BI at acute phase: Md (range)	95 (25–100)	100 (15–100)	.000	1.000
Days to 6 months examination: Md (range)	185 (160–222)	187 (171–248)	−.108	.914
NIHSS at 6 months: Md (range)	0 (0–5)[c]	0 (0–6)[b]	-,355	.722
Hemianopia at 6 months: present (%)	1 (4%)[c]	2 (7%)[b]	−.272	.785
Hemiparesis at 6 months: Md (range)	0 (0–2)	0 (0–6)	−.137	.891
Extinction/inattention at 6 months: Md (range)	0 (0–1)[b]	0 (0–1)[a]	.000	1.000
BI at 6 months: Md (range)	100 (90–100)	100 (50–100)	−.073	.942
Rehabilitation: yes/no	1/26[c]	2/25[c]	(McNemar)	1.000
Infarct location:				
ACA: present (%)	2 (7%)[a]	0 (0%)		
MCA: present (%)	20 (67%)[a]	19 (61%)		
PCA: present (%)	3 (10%)[a]	4 (13%)		
MCA+PCA: present (%)	3 (10%)[a]	1 (3%)		
ACA+MCA+PCA: present (%)	2 (7%)[a]	2 (6%)		
No MRI finding: present (%)	0 (0%)[a]	5 (16%)		

Note. T+: patients with thrombolysis; T−: patients without thrombolysis; Md: median; NIHSS: National Institution of Health Stroke Scale (range 0-34); BI: Barthel Index (range 0-100), ACA: infarct in the region of anterior cerebral artery; Rehabilitation: rehabilitation received during six-month follow-up including neuropsychological rehabilitation and/or occupational therapy; MCA: infarct in the region of medial cerebral artery; PCA: infarct in the region of posterior cerebral artery; MRI: magnetic resonance imaging.
[a]Data for 1 patient missing.
[b]Data for 3 patients missing.
[c]Data for 4 patients missing.

Table 2. Results of acute phase neuropsychological assessment and comparisons of patients with (T+) and without thrombolytic treatment (T–) matched by age, education and baseline stroke severity (NIHSS).

Variable	T– n = 31	T+ n = 31	Wilcoxon Z	*p*-value	Effect size η^2
Visual neglect: present (%)	11 (37%)[a]	4 (13%)	(McNemar)	.065	
BIT sum score: Md (range)	142 (30–146)[a]	143 (107–146)	−2.102	**.036**	.074
BIT cancelation tasks sum: Md (range)	126 (27–130)	128 (93–130)	−2.014	**.044**	.065
BIT figure and shape copying: Md (range)	4 (0–4)	4 (2–4)	−2.412	**.016**	.094
BIT line bisection: Md (range)	9 (0–9)	9 (6–9)	−2.116	**.034**	.072
BIT representational drawing: Md (range)	3 (2–3)[a]	3 (2–3)	−2.000	**.046**	.067
Number of failed BIT subtests: Md (range)	0 (0–6)[a]	0 (0–5)	−2.022	**.043**	.068
Ipsilateral orienting bias: present (%)	17 (57%)[a]	14 (45%)	(McNemar)	.581	
Starting point in star cancelation task (cm)	+1.6 (-11.9 – +13.0)	−4.2 (-11.9 – +13.9)[a]	−1.105	.269	.020
Starting point in line cancelation task (cm)	0.0 (-12.3 – +13.5)[a]	−9.6 (-11.7 – +12.2)[a]	−1.486	.137	.038
Slow processing speed: present (%)	27 (87%)	22 (71%)	(McNemar)	.180	
Cancelation time in star cancelation (s)	81 (30–171)	72 (40–210)	−.905	.365	.013
Cancelation time in letter cancelation (s)	111 (37–196)	93 (49–215)	−1.431	.153	.033

Note. T+: patients with thrombolysis; T–: patients without thrombolysis; NIHSS: National Institution of Health Stroke Scale; Md: median; BIT: Behavioral Inattention Test.
[a]Data for 1 patient missing.

Table 3. Results of 6-month neuropsychological assessment and comparisons of patients with (T+) and without thrombolytic treatment (T–) matched by age, education and baseline stroke severity (NIHSS).

Variable	T– n = 31	T+ n = 31	Wilcoxon Z	*p*-value	Effect size η^2
Visual neglect: present (%)	2 (7%)[c]	1 (3%)[a]	(McNemar)	1.000	
BIT sum score: Md (range)	142 (130–146)[d]	144 (134–146)[b]	−.846	.398	.015
BIT cancelation tasks sum: Md (range)	127 (114–130)[c]	128 (118–130)[b]	−.917	.359	.017
BIT figure and shape copying: Md (range)	4 (0–4)[c]	4 (3–4)[a]	−1.134	.257	.025
BIT line bisection: Md (range)	9 (3–9)[c]	9 (7–9)[a]	−.531	.595	.005
BIT representational drawing: Md (range)	3 (3–3)[d]	3 (2–3)[a]	−1.414	.157	.040
Number of failed BIT subtests: Md (range)	0 (0–2)[d]	0 (0–2)[b]	−.237	.813	.001
Ipsilateral orienting bias: present (%)	12 (44%)[c]	7 (24%)[a]	(McNemar)	.267	
Starting point in star cancelation task (cm)	−6.8 (-12.3 – +13.5)[c]	−11.9 (-11.9 – +13.9)[b]	−.865	.387	.015
Starting point in line cancelation task (cm)	−11.7 (-11.7 – +12.2)[c]	−11.7 (-11.7 – +13.0)[a]	−.205	.837	.001
Slow processing speed: present (%)	18 (72%)[e]	16 (57%)[b]	(McNemar)	.549	
Cancelation time in star cancelation (s)	54 (31–167)[e]	56 (33–162)[c]	−.308	.758	.002
Cancelation time in letter cancelation (s)	110 (66–186)[e]	82 (22–187)[b]	−2.286	**.022***	.109

Note. T+: patients with thrombolysis; T–: patients without thrombolysis; NIHSS: National Institution of Health Stroke Scale; Md: median; BIT: Behavioral Inattention Test.
[a]Data for 2 patients missing.
[b]Data for 3 patients missing.
[c]Data for 4 patients missing.
[d]Data for 5 patients missing.
[e]Data for 6 patients missing.

Neuropsychological variables at the acute phase

Medians and ranges of the neuropsychological variables and comparisons of T + and T– groups at the acute phase are presented in Table 2. Visual neglect was found in 11 T– patients (37%) and in 4 T + patients (13%). A borderline significance suggested less visual neglect in the T + group. Each BIT score (BIT sum score, cancelation tasks sum score, figure and shape copying, line bisection, representational drawing) was significantly lower and the number of failed BIT subtests significantly higher in the T– group than in the T + group. The effect size calculations showed medium effects for all six BIT analyses. No significant difference was found according to occurrence of ipsilateral orienting bias, which was shown by 17 T– patients (57%) and 14 T + patients (45%). Neither did the groups differ significantly according to the starting points of the line or star cancelation tasks (small effects for both starting point analyses). Slow processing speed was present in 27 T– patients (87%) and in 22 T + patients (71%). This difference was not statistically significant. There were also no significant differences between the groups in cancelation times in the star or letter cancelation tasks (small effects for both processing speed analyses).

Neuropsychological variables at 6 months

Medians and ranges of the neuropsychological variables and comparisons of T + and T– groups at 6 months are presented in Table 3. Visual neglect was still present in 2 T– patients (7%) and in 1 T + patient (3%). The groups did not differ significantly according to occurrence of visual neglect. Neither did the groups differ significantly according to any BIT scores (BIT sum score, cancelation tasks sum score, figure and shape copying, line bisection, representational drawing) or the number of failed BIT subtests (non to small effects). Ipsilateral orienting bias was shown by 12 T– patients (44%) and 7 T + patients (24%). This difference was not statistically significant. There were also no significant group differences in the starting points in the line or star cancelation tasks (non to small effects). Slow processing speed was present in 18 T– patients (72%) and in 16 T + patients (57%). This difference was also not significant. The groups did not differ according to cancelation time in the star cancelation task (no effect), but the T– group was significantly slower than the T+group in the letter cancelation task (medium effect).

Discussion

The focus of our study was to investigate whether RH infarct patients with thrombolytic treatment (T+) and without thrombolytic treatment (T-), matched for baseline stroke severity, age and years of education, differ in the occurrence of and recovery from visual neglect during a follow-up period of 6 months. In order to gain increased sensitivity for evaluating the neglect syndrome, we used the measures of cancelation time and starting point alongside the conventional assessment methods in order to additionally examine symptoms often associated with the syndrome, namely initial ipsilateral orienting bias and slowed processing speed.

At the acute phase of RH infarct, visual neglect was present in just 13% of the thrombolytic-treated patients, while for the non-thrombolytic patients the occurrence was almost three times as high (37%). This difference was not significant, but we found a borderline significance, suggesting/indicating a lower occurrence of visual neglect in patients with thrombolysis. In addition, the results indicated that the non-thrombolytic patients performed significantly worse than the thrombolytic patients in each conventional neglect test used, including the BIT sum score, the cancelation tasks sum score, the figure and shape copying, the line bisection and the representational drawing as well as the number of failed BIT subtests. This finding lends some further support to the existing preliminary signs presented in the introduction that thrombolysis has an association with favorable acute phase cognitive outcomes after an ischemic stroke.

The findings of the few earlier studies that have addressed the association between thrombolysis and visual neglect are somewhat inconsistent, however. Kettunen et al. (2012c), who examined acute phase visual neglect in thrombolytic and non-thrombolytic first-ever RH infarct patients, found no group difference in BIT sum scores – although they did not analyze the BIT subtests in the same detail as we did in this study. Neither did they find a significant difference in the occurrence of neglect, which was 15% in the thrombolytic group and 28% in the non-thrombolytic group. Since the criteria they applied for neglect was basically the same as in our study, the incidence in the non-thrombolytic group appeared to be slightly lower in their study, while in the thrombolytic group it was roughly the same in both studies. Nevertheless, Kettunen et al. found that thrombolysis independently predicted the absence of visual neglect, indicating that thrombolytic RH infarct patients had a lower risk of acute phase visual neglect compared to conservatively treated patients. Laihosalo et al. (2011), for their part, examined the association of thrombolysis with acute phase visuoperceptual functions in first-ever RH infarct patients. They found that thrombolytic-treated patients, even though they showed significantly less acute phase visuoconstructive deficits, did not differ from the non-thrombolytic patients according to the BIT sum score or occurrence of visual neglect. In their study, the occurrence of neglect was 11% and 21% in the thrombolytic and non-thrombolytic groups, respectively. They had a slightly stricter criterion for neglect (cutoff point ≤129 for total BIT score) than we used here, which may partly explain the lower occurrence of visual neglect reported in their study. The study by Strambo et al. (2020) investigated the outcomes of thrombolysis and thrombectomy in respect of subacute phase cognition after ischemic stroke. For every cognitive domain assessed, thrombectomy patients had a lower frequency of impaired performance than thrombolytic patients, who in turn outperformed the conservative treatment group. The three groups differed significantly according to apraxia, anterograde memory and executive functions. In terms of neglect, which was assessed with visual exploration of a picture, line crossing and line bisection, Strambo et al. reported a non-significant trend toward statistical differences between the three groups, but they presented no exact statistics on the differences between the two groups of thrombolytic and conservatively treated patients. Their patient sample was not fully comparable to ours as it contained patients with ischemic stroke from isolated posterior cerebral artery occlusion within the right or left hemisphere and some of them also had previous strokes and/or pre-stroke cognitive impairment.

In another study by Kettunen et al. (2012a), thrombolytic RH infarct patients showed significantly less acute phase ipsilateral orienting bias in the line cancelation task than those receiving conservative treatment. In addition, they found a trend toward significance in the star cancelation task. In our study, we found no such statistical differences. The occurrence of acute phase ipsilateral orienting bias was percentually slightly lower in thrombolytic than non-thrombolytic patients (i.e. 45% vs. 57%, respectively), but this difference was not significant either. However, the outcome measures used in our study and in the study by Kettunen et al. (2012a) were slightly different since the starting points in their study were dichotomously classified as left- or right-sided, while we used a more exact measure of distance from the midline. This might go some way toward explaining the different findings of these two studies.

As stated earlier, slowed processing speed has generally been seen as a typical symptom after RH lesions (Corbetta & Shulman, 2011; Farnè et al., 2004; Gerritsen et al., 2003; Heilman et al., 1993). This was also true in our study, where high proportions of patients in both groups – 71% in the thrombolytic and 87% in the non-thrombolytic group – showed slow processing speed in cancelation tasks at the acute phase of ischemic stroke. The percentual difference in the occurrence of slow processing speed between the groups was quite small, however, and the groups did not differ significantly in any processing speed measures at the acute phase.

At six months, the two patient groups no longer differed significantly according to any conventional measurements of visual neglect. In fact, the percentage of patients showing visual neglect had decreased among both thrombolytic and non-thrombolytic patients, and was only 3% and 7%, respectively. This is in line with the earlier notion that the most distinct neglect symptoms typically recover within the first months after stroke (Cassidy et al., 1998; Nijboer et al., 2013). The long-term cognitive outcomes after thrombolytic treatment have as yet received very limited research attention. Nys et al. (2006) investigated the effects of thrombolytic treatment on functional outcome and cognition, including visual neglect, at six to ten months after a first-ever ischemic stroke. They found that the treatment had a long-term association with beneficial functional outcome (i.e. basic and instrumental activities of daily living), but no such association was found with cognition. In their study, neglect was assessed with only a single task (star cancelation). Altogether, cognition contained seven separate domains (abstract reasoning, verbal and visual memory, executive functioning, visual perception and construction, language and unilateral neglect), but was analyzed using a single compound variable covering all these domains. Therefore, no specific implications for any particular domain, including neglect, can be derived. However, Nys et al. contemplated that thrombolysis may be associated with beneficial short-term cognitive outcomes, but this effect may disappear over time as even conservatively treated patients gradually recover. This idea is supported by the findings of our study.

Our study also supports the previous findings that RH patients may, however, show ipsilateral orienting bias and/or slowed processing speed as residual symptoms for several months post-stroke (Kettunen, Nurmi, Dastidar, et al., 2012; Mattingley et al., 1994; Nurmi et al., 2018; Samuelsson et al., 1998; Viken, 2013). Indeed, although the occurrence of ipsilateral orienting bias in our study had decreased to some degree during the first six months, the symptom was still present in one fourth of the thrombolytic patients (24%) and almost half of the non-thrombolytic patients (44%). No measures of ipsilateral orienting bias showed statistically significant differences between the thrombolytic and non-thrombolytic groups at six months.

Similarly, the occurrence of slowed processing speed decreased somewhat during the follow-up, but still the symptom was very common, as it was shown by more than half of the thrombolytic patients (57%) and by a clear majority of the non-thrombolytic patients (72%) at 6 months. Again, the two groups did not differ significantly according to the occurrence of slowed processing speed. However, the non-thrombolytic patients were significantly slower than the thrombolytic patients in the letter cancelation task six months post-stroke. Since no such differences were found at the acute phase, it is possible that the potential association of thrombolysis with a favorable processing speed outcome became more explicit after the flagrant neglect symptoms were resolved. In addition, as the groups did not differ according to cancelation time for the star cancelation task, it is possible that the more demanding letter cancelation task (which involves searching for two different stimuli, for example), was able to better reveal this residual symptom. As stated, the association of thrombolysis with long-term cognitive outcomes has as yet received very limited research attention, and none of the studies have considered processing speed. To the best of our knowledge, our study is the first to provide some indication of a possible long-term association between thrombolytic treatment and beneficial processing speed outcome, i.e. a faster performance in visual search at six months after a RH ischemic stroke.

The strengths of our study comprise a moderately large homogeneous group of consecutive patients with a first-ever RH infarct and strict criteria for both inclusion in the study and matching the patients according to baseline stroke severity, age and education. In addition to using conventional methods for assessing visual neglect, we also aimed to examine this phenomenon with more recent procedures that allow for more sensitive neglect assessment, including measurements of processing speed and starting point for cancelation (Azouvi et al., 2006; Bonato, 2012; Nurmi et al., 2010; 2018; Samuelsson et al., 1996; van Kessel et al., 2010). In this way we were able to take a broader view on visual neglect and associated symptoms, i.e. ipsilateral orienting bias and slow processing speed, which are all known to cause difficulties in basic and more complex ADL and to predict poor functional recovery (Bonato, 2012; Di Monaco et al., 2011; Jehkonen et al., 2006; Nys et al., 2005; Viken et al., 2014; Webster et al., 1995). In addition to examining the occurrence of symptoms at the acute phase of ischemic stroke, we also studied spontaneous recovery from these symptoms during the follow-up period of six months. Our purpose with this was to increase understanding of a topic that still has received very limited research attention, that is the short- and long-term cognitive outcomes after thrombolytic treatment.

Overall, the association of thrombolysis with visual neglect and cognition in general remains poorly understood and the evidence is inconsistent, and more research is clearly warranted. This study is an early-phase explorative study, and the outcomes and statistical tests regarding them do not have equal importance, and therefore we chose to control type 1 error rate informally rather than strict control (e.g. Bonferroni correction). Due to the lack of multiplicity correction, results that are close to the level of significance, could actually be type 1 errors. Therefore, the results must be interpreted with caution and treated as indicative rather than conclusive.

It is important to note that slowed processing speed may be reflective of several cognitive and motor factors and that it is not a symptom specific to neglect syndrome. When using paper-and-pencil measures of processing speed, the metric can be confounded by other factors such as visuo-spatial and executive functions, memory and fine motor control, which may also contribute to prolonged test performance. In addition, as cancelation tasks have not been conventionally used to assess processing speed, the findings should be interpreted with caution. Future research to verify these findings should indeed apply more sophisticated, computerized methods for assessing processing speed and more explicitly address the possible confounding effects of other likely factors in processing speed analyses. In addition, since ipsilateral orienting bias and slowed processing speed may occur for a long time after RH stroke, longer follow-up periods are needed in order to discover the association of thrombolysis with more thorough recovery from these symptoms.

It should be noted that the contraindications for thrombolysis may cause some bias in the characteristics of the patients and influence on the occurrence of neglect symptoms as well as other cognitive deficits. For example, the effects of prolonged and uncontrolled pre-stroke hypertension might increase an overall risk for poorer stroke outcomes and recovery. In this study, patients with previous neurological diagnosis (e.g. small vessels disease) or significant cerebral atrophy were excluded from the study. However, there may be more subtle changes present that still can affect stroke outcome. On the other hand, another thrombolysis contraindication, i.e. too mild or resolving stroke symptoms might indicate less probability for occurrence of or faster recovery from neglect symptoms. In our study, however, T + and T– groups did not differ according to overall stroke symptom severity on arrival to hospital. Instead, at the acute phase after T + patients had received thrombolytic treatment, the T– group showed more severe stroke than the T + group. Thus, it appears that in this study the T– group did not show milder nor faster resolving stroke symptoms compared to the T + group. It should also be noted that as we only examined left visual neglect in first-ever RH infarct patients, the findings of this study cannot be generalized to a more clinically representative population with different infarct sites, previous strokes or different neglect subtypes, for example. In addition, as is typical of clinical trials in general, we also saw some attrition of participants during the follow-up, specifically in the T– group. This might have had some impact on the results by concealing the possible effects of the treatment.

In conclusion, the results of our study provide some indication that thrombolytic patients show less visual neglect symptoms at the acute phase and faster performance in visual search at 6 months compared to non-thrombolytic patients after a RH ischemic stroke. These results support the existing preliminary signs of an association between thrombolysis and favorable short-term cognitive outcomes but also offer initial indications of a possible long-term association between thrombolytic treatment and beneficial cognitive outcome after a RH ischemic stroke.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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