JANI KETTUNEN

Visual Neglect and Orienting Bias in Right Hemisphere Stroke Patients with and without Thrombolysis

ACADEMIC DISSERTATION
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ABSTRACT

Thrombolysis is standard pharmacological treatment for patients with acute ischemic stroke. It significantly improves outcome when administered within three hours of stroke onset. However, knowledge remains limited about the frequency and severity of cognitive disorders after thrombolytic treatment at the acute phase of right hemisphere stroke. To help fill this knowledge gap, the present series of studies explores the association between visual neglect and thrombolytic treatment, focusing specifically on rightward orienting bias, one of the main manifestations of visual neglect. In addition, it reviews the various methods used in assessing visual neglect.

The review in Study I demonstrated differences in the accuracy of the methods used. There were also differences in patient selection and the timing of assessments of visual neglect. Neglect was assessed with a wide variety of tests. A standardized battery of neglect tests was administered in 16 studies, while four studies used two or more separate tasks. Only four studies made a distinction between subtypes of neglect. The reported prevalence of neglect is probably affected by the range of assessment methods used.

The original studies showed that patients without thrombolytic treatment had a higher risk of visual neglect (Study II) and showed more evidence of rightward orienting bias (Study IV) than patients receiving thrombolytic treatment. Comparisons of healthy controls and patients with or without thrombolytic treatment revealed differences in orienting bias. Healthy controls seemed to be more leftward biased than patients receiving thrombolytic treatment (Study IV). This suggests that a short period of recovery from right hemisphere stroke with thrombolytic treatment is not enough to repair defective rightward orienting bias at the acute phase of stroke.

Study III showed that in patients not receiving thrombolysis, the intensity of rightward orienting bias and the presence of visual neglect declined as a function of time, but differences were still found between healthy controls and patients. Both studies (III-IV) reported evidence of rightward orienting bias in patients with and without thrombolytic treatment and visual neglect.

Based on these results it is suggested that thrombolysis independently predicts absence of visual neglect and might reduce the presence of rightward orienting bias in the acute phase of stroke. Visual neglect is likely to improve over time, although symptoms of rightward orientation bias are still detected. These results on orienting bias shed further light on residual symptoms of attention difficulties after right hemisphere stroke. It is therefore suggested that for clinical purposes, orienting bias should be systematically measured after stroke.

LIST OF ORIGINAL PUBLICATIONS

This dissertation consists of the following four publications, which are referred to in the text by their Roman numerals I-IV:

I Jehkonen, M., Laihosalo, M., & Kettunen J. E. (2006). Impact of neglect on functional outcome after stroke – a review of methodological issues and recent research findings. *Restorative Neurology and Neuroscience*, *24*, 209-215.

II Kettunen, J. E., Nurmi, M., Koivisto, A-M., Dastidar, P., & Jehkonen, M. (2012). The presence of visual neglect after thrombolytic treatment in patients with right hemisphere stroke. *The Scientific World Journal,* DOI:10.1100/2012/434120

III Kettunen, J. E., Nurmi, M., Dastidar, P., & Jehkonen, M. (2012). Recovery from visual neglect after right hemisphere stroke: Does starting point in cancellation tasks change after 6 months? *The Clinical Neuropsychologist*, *26,* 305-320.

IV Kettunen, J. E., Laihosalo, M., Ollikainen, J., Dastidar, P., Nurmi, L., Koivisto, A-M., & Jehkonen, M. (2011). Rightward bias in right hemisphere infarct patients with or without thrombolytic treatment and in healthy controls. *Neurocase, 18,* 359-365.

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1. INTRODUCTION

1.1 Stroke

Stroke is a major cause of death and long-term disability in all western societies (e.g. Murray & Lopez, 1997). Worldwide, some 80% of all strokes are ischemic in origin, caused by in situ thrombosis, embolism, or systemic hypoperfusion (Feigin, Lawes, Bennett, Barker-Collo, & Parag, 2009; Roger et al., 2011). Ischemic stroke results from vascular occlusion that reduces cerebral blood flow to the area of brain perfused by the occluded artery. If the reduction in blood flow is sufficiently severe and prolonged, a series of events will occur at the cellular level that leads to infarction, including lack of glucose and oxygen supply. Ischemia is defined as a decrease in blood flow to tissues that prevents adequate delivery of oxygen, glucose and others nutrients (Bretón & Rodríguez, 2012).

According to a nationwide stroke database, the mean annual number of incident stroke patients treated in Finnish hospitals in 1999-2007 was around 11,000, 79% of whom suffered an ischemic stroke (Meretoja et al., 2010). Most ischemic strokes are localized in the area of the middle cerebral arteries (Ng, Stein, Ning, & Black-Schaffer, 2007), causing the most frequently encountered stroke syndrome with contralateral weakness, sensory loss, and depending on the hemisphere, possibly involving either language disturbance or impaired spatial perception (Caplan & Bogousslavsky, 1995).

1.1.1 Cognitive disorders after stroke

It is well established that ischemic cerebral stroke is often followed by various cognitive symptoms. The extent and type of these symptoms depend on the side, exact location and size of the infarction and on the time of assessment. Tatemichi et al. (1994) report in their study of stroke patients aged 60 or over that 78% showed impairment in one or more cognitive domains within three months of stroke onset. Hochstenbach, Mulder, Van Limbeek, Donders and Schoonderwalt (1998) suggest that stroke has a massive effect on many cognitive processes, most notably reflected in a general slowing of information processing and attention deficits.

Nys et al. (2007) also report that cognitive impairments are common consequences of acute stroke. Within three weeks of a first left or right hemisphere stroke, 74% of patients demonstrated acute impairment in at least one cognitive domain. Deficits in executive functioning, abstract reasoning, verbal memory and language were most common after left hemisphere stroke. In patients with right hemisphere stroke, the most common cognitive impairments were disorders in executive function, visual perception, construction and attention (Nys et al., 2007). According to this study 52% of right hemisphere patients and 29% of left hemisphere patients with cortical stroke showed neglect.

1.2 Visual neglect

1.2.1 Definition of visual neglect

The ability to safely navigate and to interact successfully with a complex environment (i.e. to orient towards interesting events or to search for targets) is crucial to everyday life. The precise and efficient control of such actions depends heavily on visual information. We need to have the ability to select, shift attention between different elements and process behaviourally relevant stimuli while ignoring the rest of the scene (Chechalez, Rothstein, & Humpreys, 2012). The cognitive processes underlying these abilities are collectively known as visuospatial attention. After right hemisphere stroke, the ability to attend to stimuli in the environment can be diminished as a consequence of visual neglect.

The hallmark of the neglect disorder is a failure to report, respond or orient to stimuli on the contralesional side of space that cannot be accounted for by primary sensory or motor deficits (Halligan, Cockburn, & Wilson, 1991; Robertson & Halligan, 1999). Patients with neglect can be unaware of sights, sounds, touches and body parts on the contralesional side even though they are not blind, deaf or insensitive on that side (Driver & Vuilleumier, 2001). Severe neglect patients may behave as if the left side of the world has ceased to exist (Mesulam, 1981).

The literature uses various terms to describe neglect, such as unilateral neglect, hemineglect, and hemispatial neglect. In this dissertation the term visual neglect is used because the exclusive focus of this study is on problems in the visual modality.

1.2.2 Spatial representation and range of space in visual neglect

Visuospatial information is processed in different frames of reference according to the specific demands of the ongoing behaviour (Saj & Vuilleumier, 2007). Visual neglect occurs in two spatial reference frames: egocentric (errors on the contralesional side of the viewer) and allocentric (errors on the contralesional side of individual stimuli irrespective of the side of the viewer) (Adair & Barrett, 2008; Corbetta & Shulman, 2011; Halligan, Fink, Marshall, & Vallar, 2003; Hillis, 2006; Medina et al., 2009). Allocentric spatial representation refers to representations of space both in object-centred and in stimulus-centred coordinates. Egocentric spatial representations of an object, then, depend on the object's position relative to the viewer's body (such as trunk, head or eyes) (see e.g. Grimsen, Hildebrandt, & Fahle, 2008; Hillis, 2006; Medina et al., 2009). Therefore, when someone says that a right hemisphere stroke patient is neglecting the right side, it is important to clarify, “the right side of what?” (Hillis & Rapp, 1998).

Neglect disorders vary in nature and can comprise personal, peripersonal, extrapersonal and representational domains of space (Robertson & Halligan, 1999). Personal space is the space of the body surface; peripersonal space is defined as the space within arm's reach; and extrapersonal space is the space that is beyond arm's reach (Halligan et al., 2003). This classification is widely used in the clinical assessment of visual neglect (Ting et al., 2011). Peripersonal neglect refers to neglect symptoms in the reaching space around the patient (Robertson & Halligan, 1999). Most tests are designed to evaluate visual neglect in the peripersonal space (e.g. visual scanning and cancellation tasks), and the sensitivity of different visual neglect tests varies according to their ability to measure the underlying deficits (Azouvi et al., 2002; Lindell et al., 2007; Maeshima et al., 2001). There is evidence that different forms of neglect are associated with different brain lesion sites (Aimola, Schindler, Simone, & Venneri, 2012; Committeri et al., 2007; Keller, Shindler, Kerkhoff, von Rosen, & Golz, 2005).

1.2.3 Theoretical background of visual neglect

Visual neglect can be associated with lesions of a wide range of neocortical and subcortical structures. It is thought that neglect is prompted by a right hemisphere lesion of the inferior parietal lobule, the temporoparietal junction or the inferior frontal cortex

(Halligan et al., 2003; Husain & Kennard, 1996; Marshall, Fink, Halligan, & Vallar, 2002; Mort et al., 2003; Vallar, 2001), the right superior temporal cortex (Karnath, Ferber, & Himmelbach, 2001; Karnath, Fruhmann, Kuker, & Rorden, 2004) or a number of subcortical regions (thalamus, basal ganglia, white matter fibre tracts) (Vallar & Perani, 1986; Marshall et al., 2002; Perani, Vallar, Paulesu, Alberoni, & Fazio, 1993). Mesulam (1981, 2002) proposes that the neural substrate for directed attention includes the frontal, parietal and cingulate cortices and that the neglect syndrome is caused by dysfunction in this neural network. In short, this means that a number of anatomically separate but interconnected regions are collectively responsible for the complex function of directed attention. Figure 1 shows the main anatomical areas in the right hemisphere of the brain that are associated with symptoms of neglect.

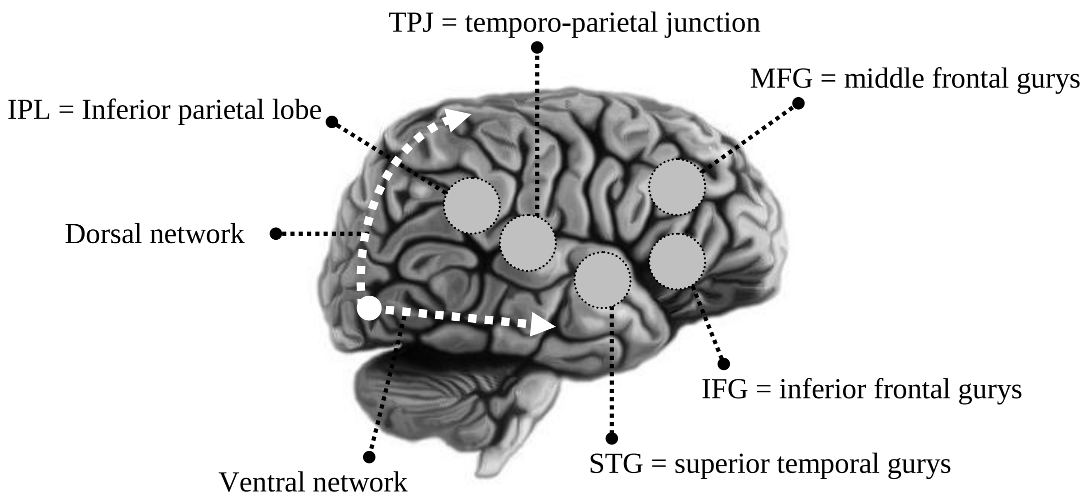

FIGURE 1. Right cortical surface of the brain and locations associated with neglect

The cognitive and neural mechanisms of neglect are described in theories of spatial attention, but the exact way in which these mechanisms work still remains disputed. There are various theories of visual neglect, which can be roughly grouped into five main categories (for an overview, see Kerkhoff, 2001). One of these categories comprises attentional theories, which are of particular importance for the present work.

Attention theories of visual neglect can be divided into two basic models: a) hemispheric rivalry or competition, and b) right hemisphere dominance for spatial processing. According to the theory of Kinsbourne (1970), each hemisphere represents the contralateral space and inhibits the other hemisphere through transcallosal pathways. Under normal conditions the activation of both hemispheres is balanced, but after stroke, the undamaged hemisphere is disinhibited from the damaged one and suppresses it. Therefore, after a right hemisphere stroke, the left hemisphere becomes relatively hyperattentive towards the right hemispace, leading to left visual neglect and ipsilesional orienting bias. In other words, the left hemisphere has stronger directional bias than the right hemisphere (Kinsbourne, 1987, 1993). This model is further supported by the work of Koch et al. (2008; 2012).

Another model of neglect reflects the right hemisphere dominance for spatial processing. It has been proposed that the right hemisphere tends to allocate attention to both hemispaces, but the left hemisphere accords attention more selectively to the right hemispace (Heilman & Van Den Abell, 1980; Mesulam 1981, 2002). Dating back some 30 years, this model says that unilateral lesions of the left hemisphere are unlikely to result in visual neglect, since the intact right hemisphere can take over the task of attending to the right side. In contrast, in the absence of similar compensatory mechanisms in the left hemisphere, right hemisphere lesions will result in marked visual neglect (Mesulam, 1981, 2002). In other words, there is redundant control of the right space by both hemispheres, whereas the left space is controlled only by the right hemisphere (Figure 2).

Mesulam (1998) restated this idea in anatomical terms: the right hemisphere contains a neural network for directed visuospatial attention that is specialized for both hemispaces, while the comparable system in the left hemisphere directes visuospatial attention only to the right hemispaces. The neural network includes lateral premotor cortex, posterior parietal cortex, cingulate cortex and subcortical areas (the basal ganglia and thalamus) (Mesulam, 1998).

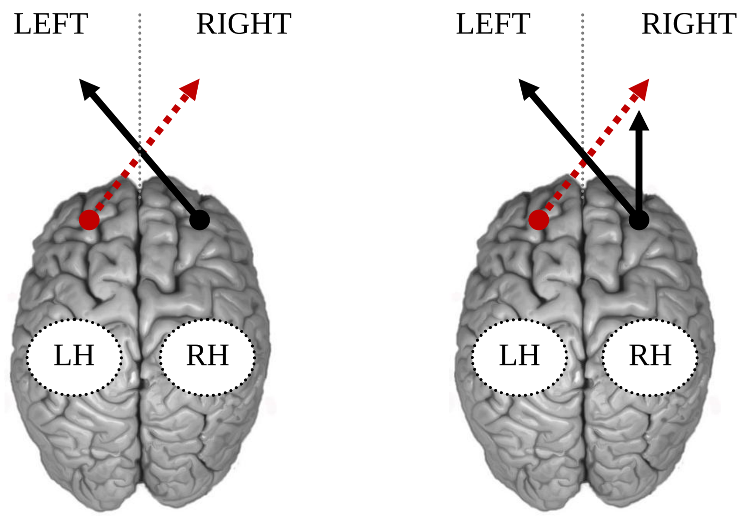

FIGURE 2. Underlying attentional mechanisms and cerebral asymmetries in the orientation of attention according to the theories of Kinsbourne (1970, 1987) and Heilman and Van Den Abell (1980). Left stands for left hemispace and right stands for right hemispace (LH=left hemisphere; RH=right hemisphere)

Corbetta, Kincade and Shulman (2002) have proposed that there are two brain networks that work together to carry out visual attentional functions. They further divide the cortical centres for spatial attention into a ventral and a dorsal network. The dorsal network is important for goal-directed, top-down selection of stimuli (includes bilaterally the intraparietal sulcus, the frontal eye field and lateral occipital complex). It is activated by directional cues and is involved in attention orientation, i.e. in preparing and applying goal-directed selection for stimuli and responses (Corbetta & Shulman, 2002). The ventral network, which is located predominantly in the right hemisphere (centred in the temporoparietal junction, anterior insula and ventral frontal cortex), is responsible and specialized for stimulus-driven, bottom-up control of attention and target detection (Corbetta & Shulman, 2002). Damage to the ventral network provokes dysfunction in the structurally intact dorsal network in the right hemisphere, resulting in a functional imbalance of evoked responses in the left and right dorsal parietal cortex (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005). Abnormal ventral-to-dorsal interactions cause an interhemispheric imbalance in the dorsal attention network and visual cortex, leading to rightward spatial biases in attention (Bartolomeo, de Schotten, & Chica, 2012; Corbetta & Shulman, 2011). This parietal imbalance is postulated as the pathomechanism of neglect (Corbetta & Shulman, 2011).

1.2.4 Prevalence and recovery from visual neglect

There has been extensive research into the prevalence of visual neglect. According to the review of this research by Bowen, McKenna and Tallis (1999), the median reported prevalence of neglect in right hemisphere patients is 43%. The variation in the reported prevalence presumably reflects differences in inclusion criteria, lesion location and assessment procedures (see Azouvi et al., 2002; Bowen et al., 1999; Maeshima et al., 2001).

Visual neglect occurs more commonly after right hemisphere than left hemisphere stroke (e.g. Bowen et al., 1999), suggesting a specialized role for the right hemisphere in directed attention (Vallar, 1993). Visual neglect does occur after left hemisphere stroke, but it often remains under-recognized, is less frequently reported, and has received less clinical and research attention (Beis et al., 2004; Kleinman et al., 2007). Ringman, Saver, Woolson, Clarke and Adams (2004) showed that 43% of right hemisphere patients and 20% of left hemisphere patients had neglect within seven days of stroke. After three months, neglect was present in 17% and 5% of the same patients. Appelros, Karlsson, Seiger and Nydevik (2002) studied 272 acute stroke patients and found that 24% of them had neglect, 32% with right and 17% with left hemisphere stroke. Among the 602 acute stroke patients studied by Pedersen, Jørgensen, Nakayama, Raaschou and Olsen (1997), 23% had neglect. Of these neglect patients, 43% had right hemisphere and 8% had left hemisphere stroke.

Increased age has been shown to be associated with a higher incidence and severity of visual neglect (Gottesman et al., 2008; Linden, Samuelsson, Skoog, & Blomstrand, 2005; Ringman et al., 2004). Ringman et al. (2004) reported that only 5% of patients aged 18-50 exhibited neglect, whereas 18% of patients aged over 80 had neglect one week post-stroke. It has been suggested (Gottesman et al., 2008) that elderly patients may have more brain atrophy and be less able to compensate for infarction. Gottesman et al. (2008) propose that older patients have specific brain changes (in the ventral and dorsal network system) that make them more vulnerable to visual neglect as a result of right hemisphere stroke. It has been suggested that the prevalence and severity of visual neglect is not influenced by gender (Kleinman et al., 2008; Ringman et al., 2004) and handedness (Ringman et al., 2004). Visual neglect is observed both in adults and in children (i.e. Laurent-Vannier, Pradat-Diehl, Chevingrad, Abada, & De Agostini, 2003).

Several clinical studies with right hemisphere stroke patients have shown that, as measured by the absence of omissions in cancellation tasks, visual neglect typically resolves over time (Appelros, Nydevik, Karlsson, Thorwalls, & Seiger, 2004; Cassidy, Lewis, & Gray, 1998; Cherney & Halper, 2001; Jehkonen et al., 2000a; Nijboer, Boudewijn, Kollen, & Kwakkel, 2013a; Stone, Patel, Greenwood, & Halligan, 1992). Patients with chronic neglect had significantly higher acute neglect severity scores than those who recovered (Karnath, Rennig, Johannsen, & Rorden, 2011). Jehkonen et al. (2010) found that poor recovery from visual neglect was a significant predictor of long-term post-stroke mortality, and that patients with visual neglect show slower functional progress in the recovery phase during rehabilitation and need longer hospitalization periods (Buxbaum et al., 2004; Cherney, Halper, Kwasnica, Harvey, & Chang, 2001). Neglect also has a significant impact on daily activities, correlating with poor recovery, return to independent living, and falls following right hemisphere stroke (i.e. Czernuszenkot & Czllonkowska, 2008; Jehkonen et al., 2001; Katz, Hartman-Maeir, Ring, & Soroker, 1999). Jehkonen et al. (2001) assessed motor, sensory and cognitive impairments in 56 right hemisphere patients within ten days of stroke. Visual neglect as assessed by the Behavioural Inattention Test (BIT) was the strongest predictor of functional recovery at one year post-stroke. The presence of visual neglect explained 73% of the total variance in activities of daily living at the three-month follow-up, 64% at six months, and 61% at one year post-stroke.

Reported recovery rates from visual neglect range from 13 to 80% (Appelros et al., 2004; Cassidy et al., 1998; Cherney & Halper, 2001; Jehkonen et al., 2000a; Nijboer et al., 2013a). This variation might be related to patient selection, lesion site, the timing of assessment, the severity of neglect, age and differences in the tasks used to evaluate neglect and recovery outcome (Azouvi et al., 2002; Cassidy et al., 1998; Gottesman et al., 2008; Jehkonen, Laihosalo, Koivisto, Dastidar, & Ahonen, 2007; Nijboer et al., 2013a, Stone et al., 1992). Stone et al. (1992) found that most neglect symptoms in right hemisphere stroke patients diminish by approximately 80% within six months. Recovery is fastest in the first seven to ten days, and reaches a plateau at three months (Nijboer et al., 2013a; Ringman et al., 2004; Stone et al., 1992). Cassidy et al. (1998) found that 68% of their patients had recovered from visual neglect at three months. They based their assessment on three cancellation tasks (line, letter and star cancellation). Jehkonen et al. (2000a) reported that 63% of their patients had recovered at six months and 75% at the one-year follow-up. In this study (Jehkonen et al., 2000a) visual neglect was assessed using six conventional BIT tasks.

Nijboer et al. (2013a) investigated 101 left or right hemisphere stroke patients in a longitudinal cohort study using two cancellation tasks (line bisection and letter cancellation). At the acute phase, 54% of these patients had visual neglect. Weekly measurements were taken during the first ten weeks, followed by biweekly measurements until the 20th week. Follow-up measurements were performed at 26, 28 and 52 weeks. Nijboer et al. (2013a) found that the time course of spontaneous recovery from visual neglect shows a natural logistic curve up to the first 12-14 weeks post-stroke. After 12 weeks, 54% of the visual neglect patients had recovered. The authors suggest that about 30-40% of visual neglect patients still suffered neglect after one year. Cherney & Halper (2001) identified two recovery subgroups in visual neglect patients: those with transient neglect from which the patients recovered within the first 6-9 months of onset, and those whose neglect persisted for more than 18 months. In this study the first assessment of visual neglect was conducted between 11 and 91 days post-onset. Jehkonen et al. (2007) explored 21 right hemisphere patients with visual neglect within ten days, and at three, six and 12 months, identifying three visual neglect recovery groups: a) continuous, b) fluctuating and c) poor recovery. The continuous group recovered within six months, whereas recovery in the fluctuating group was erratic, marked by day-to-day fluctuations (Jehkonen et al., 2007). Robertson & Manly (2002) suggest that recovery from visual neglect may reflect the use of compensatory strategies that mask a persistent distortion in the perception of space.

Karnath (1988) has earlier postulated the theory of “speed of recovery” from visual neglect and proposed a multi-component model of neglect. The multi-component model of left visual neglect postulates three separate deficits: (1) an initial automatic orienting of attention towards the right side, (2) an impairment of disengaging attention from that side and a reorienting of spatial attention towards stimuli on the left side, and (3) a more generalized reduction or slowness of information processing capacity (alertness and vigilance). Karnath (1988) proposed that the second component recovered faster than the other two. The persistence of the first and third component would therefore explain the residual deficits of visual neglect when patients have regained some contralesional orienting ability. This is consistent with the findings of different clinical studies (e.g.

Azouvi et al., 2002; Jalas, Lindell, Brunila, Tenovuo, & Hämäläinen, 2002; Pflugshaupt et al., 2004; Samuelsson, Hjelmquist, Naver, & Blomstrand, 1996).

Posner, Walker, Friedrich and Rafal (1984) suggested that patients with right hemisphere parietal lesions have a specific deficit in disengaging attention from ipsilesional stimuli, once directed to the right side. They proposed a three-stage model of attention: (1) attention is disengaged from the ipsilateral cue, (2) attention is moved to the target, and (3) attention is engaged on the target. Mark, Kooistra and Heilman (1988) tested the disengagement hypothesis of Posner et al. (1984) by comparing the performance of patients on two versions of paper-and-pencil cancellation tasks. In the first version, the patients had to mark each stimulus line on a sheet with a pencil, and in the second version they had to erase the stimuli. The patients' performance was significantly better in the line erasing than in the line marking task, indicating that the mere presence of right-sided visual stimuli appeared to induce, or at least exaggerate, left visual neglect, because the erased right sided targets cannot attract patients' attention. Similar findings were reported later by Loetscher & Brugger (2007). In a computer assessment of visual neglect, a patient was asked to use a black touch screen to represent the night sky, and to touch the locations occupied by stars. This patient put significantly more stars on the right of the screen midline, especially when stars remained illuminated after the touch (Loetscher & Brugger, 2007). Previous studies have indicated a relationship between the severity of neglect and the magnitude of disengagement deficit (Bartolomeo, Sieroff, Decaix, & Chokron, 2001; Morrow & Ratcliff, 1988).

After the recovery period, it is possible that patients who tend to start cancellation tasks from the right hemispace (early orientation bias) also manage to search for targets on the left side using compensatory right-to-left visual strategies and thus do not meet typical neglect criteria in clinically used tasks. This could mean that the measures available for assessing visual neglect are not sensitive enough to detect residual attention bias. Jehkonen et al. (2000a) proposed that patients with mild visual neglect (orientation bias) are able to anticipate their skewed spatial orientation and to compensate for visual neglect in structured and predictable circumstances. However, novel situations will often result in failures and accidents (Webster et al., 1995) and left sided collisions (Azouvi et al., 2002), or even in an increased risk of road accidents (Deouell, Sacher, & Soroker, 2005).

1.2.5 Clinical assessment of visual neglect

Several tasks are available for the qualitative and quantitative evaluation of neglect in research, clinical and rehabilitation contexts. For clinical purposes visual neglect is assessed using four main types of method: (1) paper-and-pencil tasks, (2) behavioural assessment (e.g. CBS, Catherine Bergego Scale (Azouvi et al., 2003)), (3) clinical observation, and (4) most recently, computer-based techniques (Ting et al., 2011).

Numerous clinical measures of visual neglect have been reported in the literature. Clinical tests have mainly focused on the assessment of visual neglect by means of visuomotor tasks. These cancellation and other paper-and-pencil tasks are among the most widely used methods for diagnosing visual neglect in the peripersonal space (Barrett et al., 2006). They include the line bisection task (Schenkenberg, Bradford, & Ajax, 1980), the line cancellation task (Albert, 1973), the letter cancellation task (Diller et al., 1974), the star cancellation task (Wilson, Cockburn, & Halligan, 1987a, 1987b), and Bell's task (Gauthier, Dehaut, & Joannette, 1989). In the line bisection task the patient is required to place a mark through the centre of a series of 18 horizontal lines, while in different cancellation tasks (target detection) they are asked to cross out targets (i.e. stars, bells) that are interspersed among a random array of distractors on a paper sheet (Gauthier et al., 1989; Wilson et al., 1987a, 1987b). Cancellation tasks are typically scored based on the number of targets detected and the relative frequency of omissions on the left and right sides of the paper sheet.

Despite a substantial body of research, there is still no consensus among clinicians regarding the best methods for detecting visual neglect. Only a limited number of tasks yield normative data that make it possible to differentiate between normal/healthy and impaired performance. According to Robertson and Halligan (1999), there are in all some 60 different tests of visual neglect, most of which are variants of the clinically well-established tasks (cancellation, copying and drawing). More recently Menon and Korner-Bitensky (2004) have identified 62 measures for visual neglect, 28 of which are standardized. Only two of these tasks evaluate personal space of neglect, while 20 assess the peripersonal space of neglect. It is estimated that only 13% of stroke patients are assessed using a standardized method for the evaluation of visual neglect (Menon-Nair, Korner-Bitensky, & Wood-Dauphinee, 2006).

One of the most frequently used paper-and-pencil test batteries in clinical practice and research is the Behavioural Inattention Test (BIT) (Wilson et al., 1987a). BIT was developed as a standardized screening test to determine the presence and severity of visual neglect. It consists of two types of test: six conventional paper-and-pencil tasks (BITC) and nine behavioural tasks (BITB). BITC comprises three distinct target cancellation tasks (line, letter and star cancellation), figure and shape copying, line bisection, and representational drawing. BITB, then, includes nine simulated daily living tasks: picture scanning, telephone dialing, menu reading, article reading, telling and setting the time, coin sorting, address and sentence copying, map navigation, and card sorting. Both BIT components (BITC and BITB) can be used separately in clinical settings for impairment assessments. The BITC subtests (cancellation tasks) are widely used in clinical practice as well as in research because they are easy to use for bedside screening purposes. All BITC tests are confined to the peripersonal space. The test was standardized by Halligan et al. (1991) based on a study of 54 right hemisphere and 26 left hemisphere patients and 50 healthy controls.

Since the initial development of BIT, several studies have attempted to determine which subtests might be more sensitive in identifying neglect. Studying a series of 52 right hemisphere patients, Jehkonen et al. (1998) found that the best combination of the six BITC subtests in acute phase screening was line crossing, letter cancellation and line bisection, which together identify 95% of visual neglect patients. The star cancellation task has also been described as the single most sensitive BITC cancellation task (Agrell, Dehlin, & Dahlgren, 1997; Halligan, Marshall, & Wade, 1989; Jehkonen et al., 1998; Lindell et al., 2007).

1.2.6 Visual orienting bias in right hemisphere stroke patients

Previous clinical studies (Azouvi et al., 2002, 2006; Jalas et al., 2002; Machner et al., 2012; Manly et al., 2009; Nurmi et al., 2010; Samuelsson et al., 1996) using common paper-and-pencil tasks have found that stroke patients with visual neglect use a right-to-left visual scanning strategy. This manifestation of visual neglect is known as the rightward orienting bias (later referred to as rightward bias) (Bartolomeo & Chokron, 2002; Kinsbourne, 1987).

As discussed earlier in this work (see e.g. Karnath 1988; Posner et al., 1984), rightward bias is considered an essential element of visual neglect (Bartolomeo & Chokron, 2002; Gainotti, D'Erme, & Bartolomeo, 1991; Karnath 1988; Mattingley, Bradshaw, Bradshaw, & Nettleton, 1994). Rightward bias is most clearly evident in patients with severe visual neglect, but it has also been documented in patients who have recovered form visual neglect based on chimeric face tasks, for example (Mattingley et al., 1994). Furthermore it has been established by different paper-and-pencil tasks, such as cancellation (Jalas et al., 2002; Samuelsson et al., 1996) and line bisection tasks (Bartolomeo & Chokron, 2002), but also by eye-movement recordings (Ishiai, 2006; Pflugshaupt et al., 2004) and different computerized reaction time tasks (i.e. Deouell et al., 2005; Rengachary, d´Avossa, Sapir, Shulman, & Corbetta, 2009).

Mattingley et al. (1994) tested left visual neglect patients shortly after stroke and one year later. At the second measurement after the recovery period, patients had improved scores in line and cancellation tasks, but they still showed a strong rightward bias when identifying the expression on a chimeric face. They suggest that this finding speaks for the persistence of the initial ipsilesional orientation. According to the eye-movement recordings of Pflugshaupt et al. (2004), patients with visual neglect showed ipsilateral bias in the free exploration of everyday scenes. Patients initially oriented towards the ipsilateral side (right), whereas healthy controls preferentially oriented towards the contralateral (left) side in oculumotor tasks (Pflugshaupt et al., 2004). In reaction time tasks, patients with visual neglect typically exhibit slower responses to left side than to right side stimuli (Bartolomeo, 1997; Deouell et al., 2005; Rengachary et al., 2009; Samulesson, Hjelmquist, Jensen, Ekholm, & Blomstrand, 1998).

Jalas et al. (2002) assessed 16 right hemisphere stroke patients with visual neglect, 16 right hemisphere stroke patients without visual neglect, and 31 healthy controls using seven conventional paper-and-pencil tasks. The location of the first cancellation was determined based on a dichotomous parameter (left or right). The results demonstrated that patients with visual neglect had a strong tendency to start on the right. Half of the patients without visual neglect showed rightward bias at the acute stage of stroke. Recently Machner et al. (2012) have reported similar results. In their study, 95% of patients with visual neglect showed rightward bias in the star cancellation task at the acute phase of stroke.

Samuelsson et al. (1996) assessed 60 right hemisphere stroke patients (eight of them had intracerebral hemorrhage) within one to eight weeks of stroke and later six to eight months post-stroke. Orienting bias was assessed using the same three cancellation tasks as in the study by Jalas et al. (2002). Healthy controls were used as a reference group at follow-up. Samuelsson et al. (1996) found that rightward bias was initially present in patients with and without visual neglect. After seven months of recovery, significant differences were found between healthy controls and patients with visual neglect or patients who had recovered from visual neglect in line and star cancellation tasks, suggesting that both patient groups had more rightward bias than the healthy controls. Manly et al. (2009) assessed 18 patients with visual neglect and 19 healthy controls using star cancellation tasks. They also determined the location of the first cancellation (left/right). Conducted between one and 13 months post-stroke, their assessments showed that 94% of patients with visual neglect had rightward bias, while the results for healthy controls were almost the exact opposite, with 84% showing leftward orienting bias. Earlier Azouvi et al. (2006) have also suggested that some 80% of healthy controls use a left-to-right visual scanning strategy, while the majority of visual neglect patients work in the opposite direction. They (Azouvi et al., 2002) proposed that the spatial location of the first target crossed out in paper-and-pencil tasks was the most sensitive measure of visual neglect.

1.3 Thrombolytic treatment

Thrombolytic treatment with intravenous alteplase (recombinant tissue plasminogen activator) is standard pharmacological treatment for acute ischemic stroke. In the United States it was approved for clinical use following the National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator stroke study in 1995 (NINDS, 1995). Studies of thrombolytic treatment typically define a favourable outcome as recovery with minimal or no deficits three months after treatment based on four outcome measures: a Barthel Index score ≥ 95, modified Rankin Scale score ≤ 1 (Van Sweiten, Koudstall, Visser, Schouten, & Van Ginn, 1987), Glasgow Outcome Scale of 1 (Teasdale, Knill-Jones, & Vander, 1978), and NIHSS score ≤ 1 (Goldstein, Bertels, & Davis, 1989).

The 1995 NINDS study compared patients receiving intravenous alteplase treatment with patients receiving placebo. In the first part of the study, acute ischemic left and right hemisphere stroke patients were randomly assigned within three hours of stroke onset to thrombolytic treatment (n=144) or to placebo treatment (n=147). In the second part of the study, additional stroke patients (thrombolysis, n=168; placebo, n=165) were enrolled and randomly assigned to the same groups after a three month period. Almost all of the 624 patients were treated within three hours, and 48% within 1½ hours of stroke.

The first part of the study found no differences between the two groups of patients (thromboloytic treatment vs. placebo). Outcome was defined as the proportion of patients who showed a four points or greater improvement on the NIHSS scale from baseline to 24 hours. In the second part, patients receiving thrombolytic treatment were more likely to have a favourable outcome at three months than patients treated with placebo. Compared with placebo patients, patients treated with thrombolysis were at least 30% more likely to have minimal or no disability. In part two of the study, the researchers defined good outcome as low or no deficit at three months based on four measures (Barthel Index score, Rankin Score, Glasgow Outcome, and NIHSS). The NINDS study (1995) did not report the effect of stroke laterality or the presence of cognitive disorders before or after thrombolytic treatment.

Subsequent studies (e.g. Blinzler et al. 2011; Lindsberg et al., 2003; Marler et al., 2000; Merino et al., 2007; Strbian et al., 2011; Wahlgren et al., 2007) have verified that patients who receive thrombolytic treatment within three hours of ischemic stroke can expect a favourable three-month functional outcome. Blinzler et al. (2011) found that patients with complete recovery were younger, more often male, had milder stroke symptoms, spent less time in hospital and retained a better functional outcome at three months. Their study was based on an investigation of 320 consecutive left hemisphere and right hemisphere stroke patients treated with thrombolysis within three hours of stroke onset. Based on their findings the authors suggest that up to one-fifth of acute stroke patients can achieve rapid complete recovery with thrombolytic treatment. These patients were younger and had milder stroke symptoms. Better outcome and lower mortality were sustained at three months (Blinzler et al., 2011).

Felberg et al. (2002) assessed recovery from stroke within 24 hours by using NIHSS. Recovery was defined as an improvement of $\geq$10 NIHSS points or an improvement of $\leq$3 points at the end of the hour-long infusion. They found that 22% of the stroke patients, who had middle cerebral artery occlusion, recovered from their deficits in the following order (NIHSS): gaze preference, sensation, leg motor, arm motor, face motor, aphasia and dysarthia. They noted that complete recovery was more likely in the case of deficits that tended to recover earlier. Later, Mikulik et al. (2010) showed similar results: aphasia improved very late, showed only partial response, or did not improve at all. The authors reported that the speed of recovery was variable for different neurological deficits as measured by NIHSS.

The benefit of thrombolytic treatment is thought to be due to vessel recanalization, resulting in restitution of blood flow to ischemic regions of the brain (Heiss, Thiel, Grond, & Graf, 1999; Grotta & Alexandrov, 1998), which leads to neurological improvement, smaller infarct size, and better clinical outcome (Molina et al., 2001). A shorter delay from onset of symptoms to initiation of thrombolytic treatment is also conducive to a better outcome (e.g. Hacke et al., 2004; Lees et al., 2010; Marler et al., 2000). In the study of Marler et al. (2000), patients treated with thrombolysis within 1½ hours of stroke onset had increased odds of improvement at 24 hours and a favourable three-month outcome compared to patients treated later than 1½ hours (Marler et al., 2000). Lees et al. (2010) divided patients' treatment time (stroke onset to start of treatment) into four groups: a) 0-90, b) 91 to 180, c) 181 to 270, and d) 271-360 minutes. Their analysis showed that the greatest benefit comes from earlier treatment. About one in three patients treated within three hours of symptom onset and one in six patients treated within 4.5 hours was reported to achieve significant benefits.

There are only a few studies that have investigated the benefits of thrombolytic treatment in Finnish patients (e.g. Laihosalo et al. 2011; Lindsberg et al., 2003; Losoi et al., 2012; Ruuskanen et al., 2010; Strbian et al., 2011, 2012; Strbian, Atula, Meretoja, Kaste, & Tatlisumak, 2013). Lindsberg et al. (2003) studied 75 consecutive left hemisphere (41) and right hemisphere (34) stroke patients, 54 of whom were treated within three hours of symptom onset. At three months, 61% of the patients had reached functional independence, while 8% were severely disabled or fully dependent (Lindsberg et al., 2003). Strbian et al. (2011) had a sample of 874 consecutive patients with left and right hemisphere stroke. They found that the patients who at 24 hours showed no neurological symptoms (NIHSS score 0 = no symptoms) following thrombolysis were younger and had milder symptoms of stroke on admission. These stroke patients had an excellent outcome and lower mortality more often than others, but even so 8% of them required help with daily activities or were dead at three months after stroke onset. These studies (Lindsberg et al., 2003; Strbian et al., 2011) did not evaluate or report cognitive disorders before or after thrombolytic treatment. In the study by Strbian et al. (2012) three stroke patients with visual field defect were examined post-thrombolysis. All patients received thrombolysis within 4.5 hours, two of them within three hours. Visual field defect in both these patients, who received thrombolysis within three hours, resolved within two hours of the initiation of thrombolysis. Partial improvement was also observed at two hours post-thrombolysis in patients who received thrombolysis within 4.5 hours of stroke onset. No neuropsychological deficits were found. Unfortunately, the authors did not report what kind of neuropsychological measures they used. Ruuskanen et al. (2010) found that thrombolytic treatment is a significant predictor of earlier discharge to home in patients with moderate or severe brain infarct.

There is only limited research into cognitive outcomes in stroke patients after thrombolytic treatment (Bugnicourt, Duru, Picard, & Godefrey, 2008; Laihosalo et al., 2011; Nys, van Zandvoort, Algra, Kappelle, & de Haan, 2006; Siekierka-Kleiser, Kleiser, Wohlschläger, Freund, & Seitz, 2006). Laihosalo et al. (2011) reported that thrombolytic treatment has a favourable effect on visuoperceptual functions at the acute phase of stroke. This result was based on a study of 28 matched pairs receiving or not receiving thrombolytic treatment. Bugnicourt et al. (2008) described the recovery of one patient after thrombolytic treatment. According to this case report (Bugnicourt et al., 2008) acute phase left visual neglect disappeared after thrombolysis, and at the six-month follow-up the patient had fully recovered. This study reported the presence or absence of visual neglect, but provided no information on the method used to assess visual neglect. Siekierka-Kleiser et al. (2006) investigated 52 stroke patients of whom 19 had motor hemineglect. Five patients (26%) with motor neglect recovered completely within seven days (three of them received thrombolysis), and the rest of the neglect group did not improve at all (three of them received thrombolysis). The authors (Siekierka-Kleiser et al., 2006) suggest that rapid complete recovery in motor hemineglect stroke patients may be related to thrombolytic treatment. This study covered left and right hemisphere stroke patients and did not report other modalities of neglect.

Nys et al. (2006) examined 25 patients with and 69 patients without thrombolytic treatment. They found evidence of favourable effects on functional outcome, but no effects on any cognitive domain during the six to ten-month follow-up. This study did not report on lesion laterality or the presence of visual neglect, even though visual neglect was assessed with star cancellation task. The authors suggest that thrombolytic treatment potentially has a short-term effect on cognitive outcome, but this effect is not sustained over time.

2. AIMS OF THE STUDY

Although thrombolysis is one of the most beneficial treatments after acute stroke, cognitive outcomes are not always satisfactory. However, most research into the neurological consequences of stroke focuses on functional or clinical impairments. The severity and frequency of cognitive disorders after thrombolytic treatment continue to remain poorly understood.

This thesis presents a detailed clinical investigation of visual neglect after a first-ever right hemisphere stroke in patients with and without thrombolytic treatment. Special attention is given to rightward orienting bias, one of the main manifestations of visual neglect after right hemisphere stroke.

The aims of this study are:

1) to review earlier research exploring the assessment methods of visual neglect (Study I);

2) to investigate the prevalence of visual neglect after right hemisphere stroke in patients with and without thrombolytic treatment (Study II);

3) to investigate visual orienting bias in patients with and without visual neglect at the acute phase and at a six-month follow-up (Study III), and

4) to investigate visual orienting bias in patients with and without thrombolytic treatment at the acute phase of stroke, and to compare the results of treated patients and healthy controls (Study IV).

3. METHODS

3.1 Review of earlier studies

The MEDLINE and PSYCHLIT databases were searched for relevant articles published between January 1996 and August 2005 using the search terms "stroke, neglect, perceptual disorders, and daily living". The exclusion criteria were as follows: a) non-English articles, b) studies on non-human subjects and c) non-adult subjects (< 19 years), and d) articles published before January 1996. After these exclusion criteria were applied, 337 articles remained. The abstracts of all of them were read by all three authors. Next, studies exclusively concerned with the effects of a specific intervention method, case reports, studies failing to specify any functional outcome measure after stroke, theoretical articles or reviews, and experimental studies were excluded. Neither book chapters nor published letters were included. These criteria were met by 22 of the 337 abstracts. The lists of references of these 22 articles were searched, yielding four additional articles. The total number of articles reviewed was thus 26. All these articles were checked by three independent reviewers, all of whom took part in evaluating the content of these articles. There were no disagreements among the independent reviewers regarding the selection or content of the articles in this study.

3.2 Original studies

3.2.1 Patients

The patients included in the original studies were admitted as emergency cases to Tampere University Hospital between June 2005 and June 2008. The patients were first screened and interviewed at the neurological ward to make sure they met the initial inclusion criteria: no previous history of neurological, cognitive or psychiatric disorders, no alcohol abuse, no severe primary visual or auditory impairment, no left-handedness, no decreased level of consciousness, no pre-existing dependence in activities of daily living and age under 80 years. Decreased level of consciousness was determined by an experienced neurologist. Visual and auditory impairment were checked by the researcher in the interview situation and based on a review of the patient's medical history.

Only right-handed right hemisphere patients with first-ever stroke were included in order to avoid interference from previous lesion. Figure 3 describes the procedure of patient selection in different studies. In Studies II and IV, the sample consisted of 34 patients with and 43 without thrombolytic treatment. In Study III, the sample consisted of 10 patients with and 27 without visual neglect. The patients' characteristics in each original Study (II-IV) are presented in Table 1.

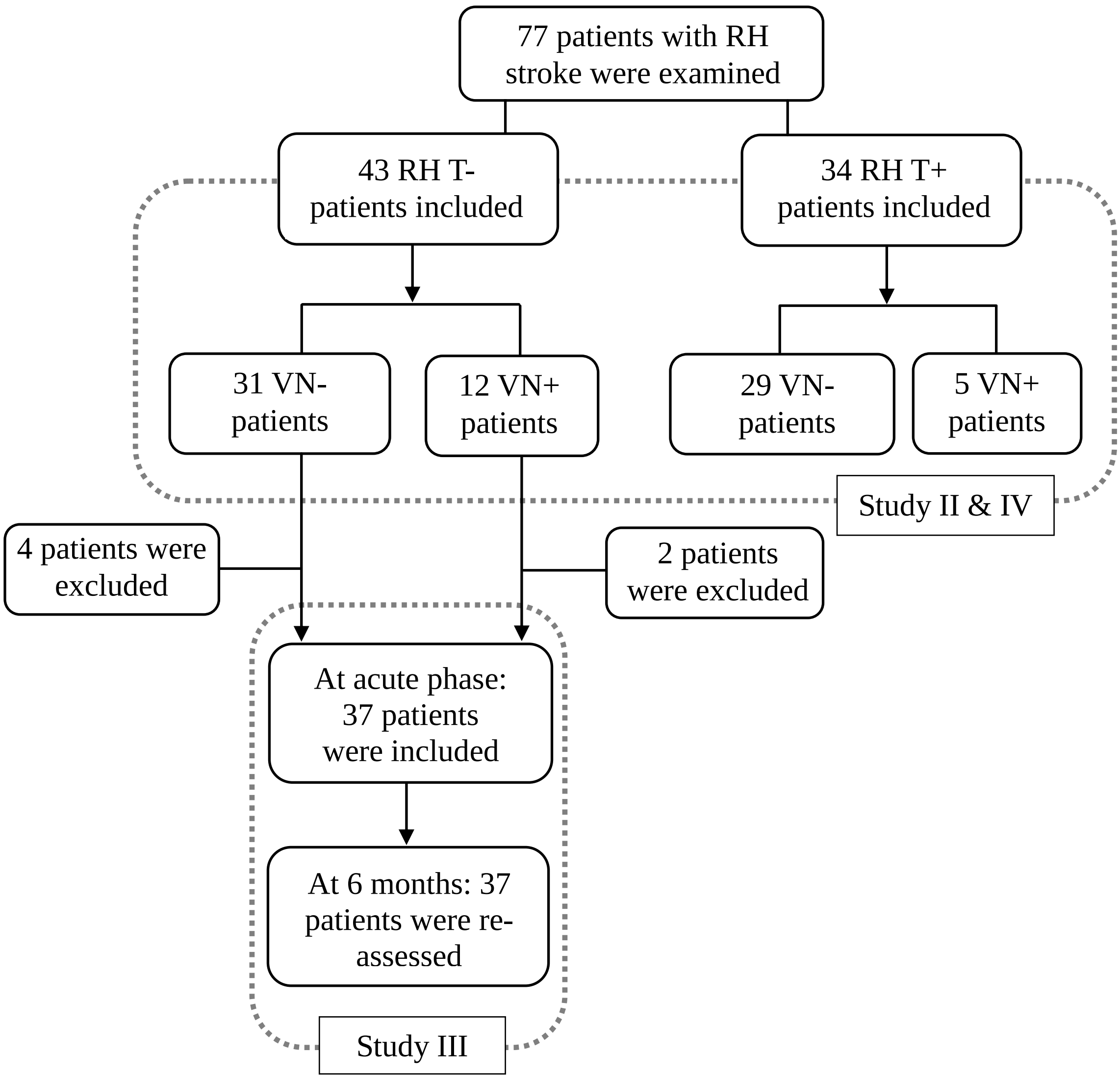

FIGURE 3. Selection of acute ischemic right hemisphere stroke patients in original Studies II-IV (RH = right hemisphere; RH T+/- = right hemisphere stroke patients with or without thrombolytic treatment; VN+/- = presence or absence of visual neglect)

Table 1. Clinical characteristics of right hemisphere stroke patients in Studies II-IV

Descriptive variables	Study II & IV			Study III		
	T+ (n=34)	T- (n=43)	Difference[1]	VN+ (n=10)	VN- (n=27)	Difference[1]
Male / female	19 / 15	31 / 12	ns	7 / 3	21 / 6	ns
Age: Md (range)	60.5 (30-77)	62.0 (36-79)	ns	65 (56-79)	62 (36-78)	ns
Education (years): Md (range)	10.0 (6-16)	9.0 (6-20)	ns	8.5 (6-10)	10 (6-20)	p = 0.044
MMSE: Md (range)	27.5 (20-30)	27 (21-30) [a]	ns			
BITC: Md (range)	143.5 (38-146)	142 (31-146)	ns	120.5 (31-137)	143 (132-146)	p <.001
BITC: VN present (%)	5 (15)	12 (28)	ns	100	0	
a) NIHSS: Md (range)	6.0 (1-17)	4.0 (1-15)	ns			
b) NIHSS: Md (range)	1 (0-17) [a]	3 (0-14) [b]	p = 0.009	6.5 (1-10)	2 (0-8) [b]	p = 0.001
Hemianopia: present	5 (15) [b]	5 (12) [c]	ns	1 (11)	3 (11)	ns
BI: Md (range)				75 (30-95) [a]	100 (35-100) [b]	p <.001
Infarct size: mean cm^3 (SD)				27.1 (23.5) [a]	7.1 (9.7) [c]	p = 0.013

[1] Mann-Whitney U or χ^2 test; p-value

Abbreviations: BI = sum score of the Barthel Index; BITC = sum score of six conventional subtests of the Behavioural Inattention Test; Md = median; MMSE = Mini Mental State Examination; NIHSS = sum score of the National Institute of Health Stroke Scale; ns = not significant; T+/- = patients with or without thrombolysis; VN = visual neglect; VN+/- = patients with or without visual neglect; a) = evaluated on admission in the emergency department; b) = evaluated at neurological ward; [a] missing value for one patient; [b] three patients had missing values; [c] four patients had missing values; [d] 12 patients had missing values

3.2.2 Healthy controls

In Studies III and IV, a reference sample of 49 and 62 right-handed healthy controls were used, respectively. Healthy controls were recruited from local pensioners' clubs and from among the researchers' acquaintances (family members, friends or volunteers who came to our attention by word of mouth), and they were screened for psychiatric or neurological disorders and possible history of alcohol abuse using a semi-structured interview. The possible presence of general cognitive decline was evaluated with the Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975). MMSE is a 30-point questionnaire used for screening orientation, memory, attention, calculation and language. Scores vary from 0 to 30 (0 = severe cognitive impairments, 30 = no cognitive impairments). A score of less than 24 is considered as indicative of cognitive impairment, and therefore this was used as the cut-off score for exclusion from the study. All participants reported having normal or corrected-to-normal vision, were native speakers of the Finnish language, and were blind to the hypotheses of the study.

Table 2. Clinical characteristics of healthy controls in Studies III and IV

Descriptive variables	Study III (n=49)	Study IV (n=62)
Male / female	21 / 28	32 / 30
Age: Md (range)	59 (30-80)	56.5 (30-80)
Education (years): Md (range)	11 (5-17)	12.5 (5-26)
MMSE: Md (range)	28 (25-30)	29 (25-30)

Abbreviations: Md = median; MMSE = Mini Mental State Examination

3.3 Clinical assessment of visual neglect and orienting bias

3.3.1 Assessment of visual neglect

The presence of peripersonal visual neglect was assessed using the six conventional BITC paper-and-pencil subtests (Wilson et al., 1987a). This test battery is well documented, frequently used in visual neglect studies, and it is simple to administer and score. Furthermore, it has been standardized and used previously for Finnish patients (Jehkonen, 2002; Jehkonen et al., 1998). Original cut-off points were used to make it comparable with earlier studies. 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 BITC subtests were considered to have visual neglect. For each subtest the same cut-off points were used as recommended by Halligan et al. (1989). General cognitive function was evaluated with the Mini Mental State Examination (Folstein et al., 1975) in Studies II and IV.

3.3.2 Assessment of visual orienting bias

Orienting bias was assessed using the three BITC cancellation tasks (Wilson et al., 1987a). The line cancellation task consists of 40 lines randomly spaced on a landscape A4 sheet, with 18 target lines on each side of the paper and four on the midline. The patient is instructed to cross over all lines on the sheet. The letter cancellation task consists of 40 target letters (E, R) among 130 false target letters on a landscape A4 sheet. The stimuli are arranged in five horizontal rows of equal length, 34 items per row. The patient is asked to mark all the target letters. The star cancellation task consists of 56 targets (small stars) and 75 false targets (53 big stars, 13 letters and ten words), which are scattered randomly on a landscape A4 sheet. The patient is instructed to search and mark all the small stars.

Each stimulus sheet (A4; 21 cm x 29.5 cm) was placed directly in front of the patient and aligned with his or her midsagittal plane, in order to decrease any bias towards either side and to ensure standard administration. 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 (first cancellation) in each task. In Study

III the starting point was designated left or right with respect to the midline of the paper sheet, and in Study IV the distance of the starting points was measured from the centre of the page in centimetres. All patients were examined as soon as they were able to undergo the testing procedure. Tasks were performed under normal room light and no feedback was given after the tasks.

3.4 Neurological and neuroradiological examinations

3.4.1 Neurological examination and thrombolytic treatment procedure

Stroke severity was defined using the National Institute of Health Stroke Scale (NIHSS) (Goldstein et al., 1989) (range 0-34: 0-1 = none or minimal symptoms, 2-8 = mild symptoms, 9-15 = moderate symptoms, ≥16 = severe symptoms), which is the most commonly used scale for evaluating outcome in acute stroke trials. The severity of stroke was scored at pre-treatment (≤ 3 hours), on arrival at the emergency department (Study II), and later on the neurological ward within ten days of stroke onset (Studies II-IV). The presence of visual field defect was assessed using a standardized neurological confrontation technique as part of the NIHSS. Basic activities of daily living were evaluated within ten days of stroke onset using the Barthel Index (Mahoney & Barthel, 1965) (range 0-100: 0-50 = full dependency, 55-90 = moderate dependency, 95-100 = functional independence), which comprises ten items measuring feeding, bathing, grooming, dressing, bowel control, bladder control, toileting, chair/bed transfer, ambulation, and stair climbing. The maximum score implies full functional independence. A Barthel Index score of 95 or 100 was defined as a good or favourable outcome at six months. All neurological examinations were carried out by an experienced neurologist who was blind to the neuropsychological data.

Thrombolytic treatment was administered within the first three hours of stroke onset as recommended in the NINDS (1995). Exclusion criteria for thrombolytic treatment were adopted from the NINDS (1995). All treatment decisions were made by experienced neurologists. Table 3 describes the clinical assessment of visual neglect and orienting bias and neurological examination conducted in Studies II-IV.

Table 3. Overview of clinical assessment and neurological methods used in different studies

Method	Study II	Study III	Study IV
BITC	O	O	O
Analyses of orienting bias:			
Line cancellation		O	O
Letter cancellation		O	O
Star cancellation		O	O
MMSE	O		O
NIHSS	O	O	O
BI		O	

Abbreviations: BI = Barthel Index; BITC = conventional subtests of the Behavioural Inattention Test; MMSE = Mini Mental State Examination; NIHSS = National Institute of Health Stroke Scale

3.4.2 Neuroradiological examination

Computed tomography (CT) of the brain was performed one to four hours from stroke onset to verify the side and size of the infarction. Native axial 5 mm/7.5 mm slices were taken from the level of foramen magnum to the vertex of the skull on a modern 16 multi-detector CT machine (GELIGHTSPEED RT16, Wisconsin, USA). Stroke location was evaluated by an experienced neuroradiologist who was blind to the neuropsychological and neurological data.

4. RESULTS

4.1 Review of earlier neglect studies - Study I

The studies reviewed involved right hemisphere and left hemisphere brain infarct and heamorrhage patients. Only eleven studies recruited right hemisphere damaged patients, while the rest additionally included right and left hemisphere patients as well as patients whose lesion laterality was not classified.

Neglect was assessed with a large variety of paper-and-pencil tasks that measured peripersonal forms of visual neglect. A standardized battery of neglect tests (BIT or Pizzamiglio's four-test battery) was conducted in 16 studies, while four studies used two or more separate tasks (e.g. cancellation tasks, line bisection, copying and drawing). Five studies used only a single paper-and-pencil task (e.g. cancellation task, line bisection) to define neglect. One study did not specify its method of assessment. In four studies, subtypes of neglect were specified at different levels of accuracy, with evaluations presented of personal, peripersonal, extrapersonal and motor neglect. Also the terminology used in the studies reviewed lacked consistency, and very few of the studies provided a detailed definition of the concept of neglect.

Neglect was assessed for the first time between one and 378 days after stroke. The length of follow-ups ranged from two months to three years. In 11 studies the first assessment took place more than four weeks after onset. In eight studies follow-up studies were performed before three months or between six and 12 months after onset. Three studies had longer than 12-month follow-ups. Follow-ups were not conducted in three studies.

4.2 Presence of visual neglect - Study II

The population in Study II consisted of 77 right hemisphere stroke patients, 34 of whom received thrombolytic treatment. Visual neglect was present in 22% of the patients; 15% of those with and 28% of those without thrombolysis had visual neglect. Patients without thrombolytic treatment had more severe stroke than patients with thrombolytic treatment on average four days after stroke onset. Thrombolysis within three hours of stroke onset independently predicted absence of visual neglect after adjusting for years of education, gender, age and NIHSS at baseline. A higher NIHSS sum score at baseline increased the likelihood of the presence of visual neglect. Table 4 shows the independent significance of each predictor.

Table 4. Prediction of visual neglect at the acute phase of stroke

Predictor	OR	95% CI for OR	p-value
Thrombolytic treatment	4.37	0.99 to 19.17	0.05
Gender	1.89	0.48 to 7.52	ns
NIHSS	1.27	1.08 to 1.15	0.004
Age	0.99	0.94 to 1.06	ns
Education (years)	0.84	0.63 to 1.14	ns

Abbreviations: CI = confidence interval; NIHSS = sum score of the National Institute of Health Stroke Scale; OR = odds ratio; ns = not significant

4.3 Visual orienting bias in right hemisphere stroke patients - Study III

Study III included ten patients with visual neglect, 27 patients without visual neglect and 49 healthy controls. None of the 37 patients received thrombolytic treatment or had a recurrent stroke during the follow-up. At the acute phase of stroke, patients with visual neglect had more severe stroke, larger infarcts, lower BITC sum scores, were less educated, and were more dependent in basic activities of daily living than patients without visual neglect.

At baseline, patients with visual neglect were more rightward biased than patients without visual neglect in all cancellation tasks. Orienting bias in the star cancellation task and the Barthel Index sum score showed a statistically significant correlation, suggesting that rightward bias has a possible impact on daily functioning. The mean orienting biases in the three cancellation tasks are shown in Figure 4.

In patients with visual neglect the strength of visual orienting bias and the presence of visual neglect changed as a function of time. At follow-up two patients had visual neglect as measured by BITC, and rightward bias decreased significantly as compared to the baseline only in the line cancellation task.

After the recovery period, orienting bias differed between patients with visual neglect and healthy controls. In the letter cancellation and in the star cancellation tasks, healthy controls showed more leftward bias than patients with visual neglect. As can be seen in Figure 4, a significant difference in orienting bias was also found between patients without visual neglect and healthy controls in the star cancellation task. Healthy controls showed more leftward bias than patients without visual neglect. None of the other results were statistically significant.

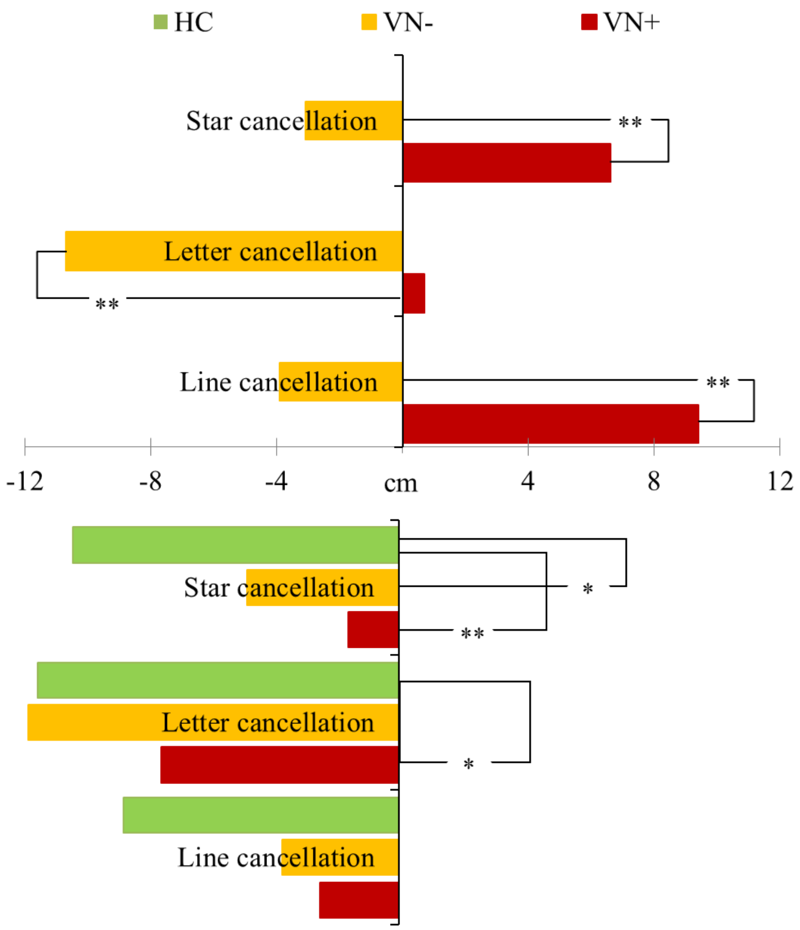

FIGURE 4. Mean starting points in the three cancellation tasks in patients with or without visual neglect (VN+/-) and healthy controls (HC). Top: at acute phase. Bottom: at follow-up. (Note: * denotes statistical significance at the level of p <.05 and ** p <.01.)

In both patient groups the follow-up results for stroke severity and basic activities of daily living showed a statistically significant improvement compared to the baseline results. A significant improvement was also found in BITC sum scores in patients with visual neglect, but not in patient without visual neglect (Table 5).

Table 5. BITC, BI and NIHSS sum scores at each assessment in patients with or without visual neglect and comparisons between the two points of measurement

Patient group	Assessment time		
	within 10 days	six months	Difference[1]
VN+ group (n=10)			
BITC: Md (range)	120.5 (31-137)	138.5 (130-145)	p = 0.012
BI: Md (range)	75 (30-95) [a]	100 (85-100)	p = 0.011
NIHSS: Md (range)	6.5 (1-10)	1 (0-6)	p = 0.007
VN- group (n=27)			
BITC: Md (range)	143 (132-146)	144 (138-146)	ns
BI: Md (range)	100 (35-100) [b]	100 (95-100)	p = 0.041
NIHSS: Md (range)	2 (0-8) [b]	0 (0-2)	p <.001

[1] Mann-Whitney U test; p-value

Abbreviations: BI = sum score of the Barthel Index; BITC = sum score of six conventional subtests of the Behavioural Inattention Test; Md = median; NIHSS = sum score of the National Institute of Health Stroke Scale; ns = not significant; VN+/- = patients with or without visual neglect; [a] missing value for one patient; [b] three patients had missing values

The results for individual tasks in the visual neglect group indicated that four patients at the acute phase of stroke and one patient at the six-month follow-up started all cancellation tasks from the right. At the acute phase of stroke four patients and at the six-month follow-up one patient started two tasks from the right. In the patient group without visual neglect, only one patient at the acute phase of stroke started three tasks from the right; five patients at the acute phase of stroke and eight patients after the six-month follow-up started two tasks from the right.

At the six-month follow-up, approximately 40% of the patients in these groups showed rightward bias in the line cancellation task. In the star cancellation task the figures were 40% and 28%. In the letter cancellation task none of the patients without visual neglect showed rightward bias, and only one patient with visual neglect showed rightward bias at the six-month follow-up. Figure 5 describes the results of orienting bias for patients with and without visual neglect in cancellation tasks.

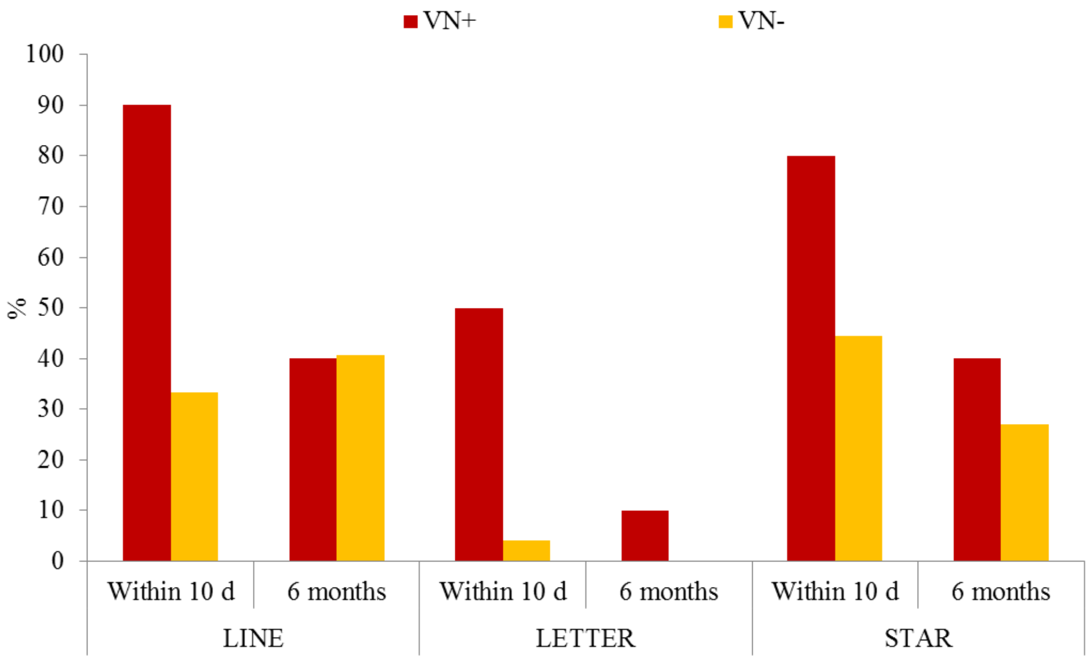

FIGURE 5. Rightward bias in patients with (VN+) or without (VN-) visual neglect within ten days of stroke and six months post-stroke in three cancellation tasks (line = line cancellation task; letter = letter cancellation task; star = star cancellation task; d = days).

4.4 Thrombolytic treatment and visual orienting bias - Study IV

The patient samples in Studies II and IV were the same. In addition, Study IV had a reference group of 62 healthy controls. The patients groups were found to differ in their visual orienting bias. Patients with thrombolytic treatment showed significantly more leftward visual orienting bias in the line cancellation task than patients without thrombolytic treatment. None of the other results were statistically significant.

Healthy controls showed a robust leftward visual orienting bias in all cancellation tasks. Statistical differences in visual orienting bias were calculated between healthy controls and patients with thrombolytic treatment. In all cancellation tasks healthy controls showed significantly more leftward orienting bias than patients with thrombolytic treatment. The results between healthy controls and patients without thrombolysis were not compared.

More detailed analyses showed that the healthy control group had significantly more leftward orienting bias than patients with thrombolytic treatment (with or without visual neglect) in all cancellation tasks. Also, a statistically significant difference was observed in the letter cancellation task between the treated patients with and without visual neglect. Figure 6 describes visual orienting biases in the three cancellation tasks for healthy controls and treated patients with and without visual neglect.

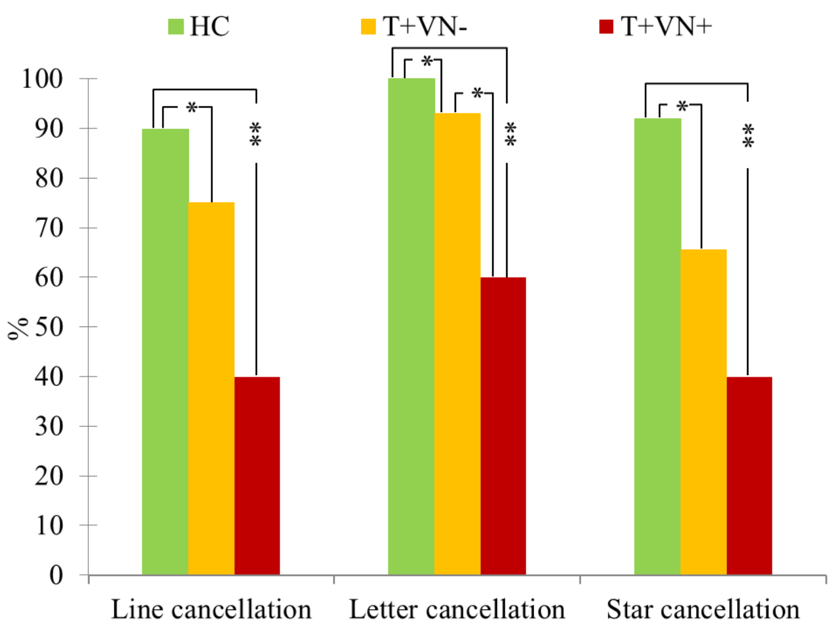

FIGURE 6. Percentage of leftward visual orienting bias in three cancellation tasks in patients with thrombolysis with (T+VN+) or without visual neglect (T+VN-) and in healthy controls (HC). (Note: * denotes statistical significance at the level of p <.05 and ** p <.01.)

5. DISCUSSION

The present series of studies is concerned with the association between visual neglect and thrombolytic treatment in first-ever right hemisphere stroke patients with and without thrombolytic treatment. Special focus is given to rightward visual orienting bias, one of the main manifestations of left visual neglect. In addition, the methods used in the clinical assessment of visual neglect are reviewed.

The following discussion begins by reviewing the results of previous studies. It then proceeds to assess the clinical implications of the present results, and finally to consider future directions for research.

5.1 Review of earlier neglect studies

According to the review conducted in Study I, a standardized test battery was used to assess visual neglect in 16 studies, and five studies used a single paper-and-pencil task. The time intervals from stroke to the first assessments and from first assessment to follow-up as well as patient selection differed markedly between the studies.

It is well established that no single paper-and-pencil cancellation or other visual neglect task covers all clinical forms of visual neglect (Appelros, Karlsson, Seiger, & Nydevik, 2003), and that one task it is not enough to detect visual neglect (e.g. Azouvi et al., 2002, 2006). The sensitivity of single tests in detecting visual neglect varies widely from 19% to 51% (Azouvi et al., 2002). Therefore, it is recommended that a multifactorial approach be adopted in the clinical testing of visual neglect (Azouvi et al. 2006; Halligan et al., 1989). Bowen et al. (1999) proposed in their meta-analysis that the prevalence of visual neglect varies widely depending on the assessment methods used, and therefore the use of standardized tests is conducive to more reliable results. If the same tests are used, frequency rates can be compared across different studies (Bowen et al., 1999). One possible reason for the differences seen in the reported frequencies of visual neglect lies in the way in which neglect subtypes are defined.

Many of the studies reviewed here failed to specify which subtype of neglect they were measuring (or offered a poor characterization of the pattern of neglect). Only four studies made a distinction between subtypes of neglect. The reason for this probably lies in the fact that the most commonly used cancellation tasks are insensitive to subtypes of neglect and to subtle or mild forms of neglect (Barrett et al., 2006). On the other hand, Keller et al. (2005) suggest that cancellation tasks are based on an egocentric reference system responsible for visuospatial attention. Buxbaum et al. (2004) observed a dissociation of personal and peripersonal neglect (and also motor and perceptual neglect). Appelros et al. (2002, 2004) and Farné et al. (2004), on the other hand, evaluated personal, peripersonal and extrapersonal neglect. It is important to note that none of the studies reviewed reported distinct subtypes of neglect defined by two spatial frames of reference: egocentric and allocentric.

The issue of visual neglect subtypes is important, as there is some evidence that patients with different symptom profiles may respond differently to treatments or rehabilitation programmes (i.e. Pierce & Buxbaum, 2002). Information about different of neglect subtypes can be useful in planning strategies to ameliorate different forms of visual neglect (Arene & Hillis, 2007). Neglect has independent predictive value for poor functional outcome (i.e. Jehkonen et al., 2000a, 2001; Katz et al., 1999), but there is only limited evidence on the impact of different subtypes of neglect on functional outcome. In the future neglect should be divided into different subtypes of the disorder in the same way as other cognitive disorders, such as subtypes of aphasia. Identification of the spatial frame of reference or the subtype of visual neglect might help select the best rehabilitation strategy for each patient and to specify its impact on functional outcome.

An inherent problem with most clinically used paper-and-pencil cancellation tasks is that patients may be able to compensate for their deficits. Cancellation tasks differ in terms of their difficulty, and therefore some of them are better at detecting milder degrees of neglect than others. Mesulam (1981) observes that visual neglect is a problem in directed and selective attention, and therefore visual neglect patients may have difficulty selecting relevant stimuli or filtering out distractors. As the task's selective attention requirements increase, so the signs of visual neglect tend to become more apparent and performance will be poorer. Making a task more resource demanding will increase its sensitivity to detecting neglect (Barrett et al., 2006). Variations in the frequency of neglect may also occur as a result of tiredness, distractions, motivation and external cues (Bowen et al., 1999). Also the prevalence of visual neglect probably depends on the operational definition of visual neglect applied in each study (Maeshima et al., 2001).

Bonato & Deouell (2013) discuss the differences and relative benefits of computer-based and paper-and-pencil tests of visual neglect. Computer-based assessment, they conclude, has several advantages over the commonly used paper-and-pencil tasks, which they suggest suffer from various limitations. They do not change from one examination to the next, and therefore allow for learning and compensatory strategies; they are static and do not reflect the dynamic character of the natural environment; and they are typically summarized into a single score. Computerized tasks may have the advantage of being less susceptible to test-retest bias, making them suitable for recovery tracking, for instance (Kortte & Hillis, 2011).

Even though researchers have been turning increasingly to technologically more advanced and ecologically possibly more valid tasks (Kortte & Hillis, 2011), many recent studies still use standardized test batteries such as BIT for the assessment of visual neglect (Bird et al., 2006; Eschenbeck et al., 2010; Golay, Schnider, & Ptak, 2008; Grimsen et al., 2008; Karnath et al., 2011; Medina et al., 2009; Molenberghs & Sale, 2011; Ptak, Di Pietro, & Schneider, 2012; Saj, Verdon, Vocat, & Vuilleumier, 2012; Urbanski et al., 2011; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010; Vossel et al., 2011). Yang, Zhou, Chung, Li-Tsang, and Fong (2013) found in their review that BIT was used as the primary outcome measure of rehabilitation interventions or treatment programmes in 12 rehabilitation studies. This suggests that paper-and-pencil tasks are indeed still a useful tool. In general, however, it is important to stress that computerized tasks should not be seen as rival to paper-and-pencil tasks, but on the contrary as complementary of each other.

Based on the findings of this Study (I) it seems clear that differences in the reported incidence of visual neglect are due to differences in the assessment methods used, non-standardized assessment methods, heterogeneous patient cohorts, inconsistent definitions, and different timings of assessment, all of which furthermore complicate making comparisons between individual sets of results (Bowen et al., 1999; Ting et al., 2011).

5.2 Prevalence of visual neglect after thrombolytic treatment

The results from Study II indicate that the administration of thrombolytic treatment within the first three hours of right hemisphere stroke reduces the risk of visual neglect. Visual neglect was observed in 15% of patients after thrombolytic treatment. To the best of the author's knowledge, there are no earlier reports on the prevalence of visual neglect post-thrombolysis, or on the association between thrombolysis and visual neglect as assessed using a standardized battery of visual neglect tests and a systematic evaluation of a patient sample at the acute phase of stroke.

The data from Study II indicate that only 15% of patients with thrombolytic treatment showed visual neglect, which is far less than previously reported in right hemisphere patients without thrombolytic treatment (Bowen et al., 1999; Jehkonen, Ahonen, Dastidar, Laippala, & Vilkki, 2000b; Nijboer et al., 2013a; Ringman et al., 2004). In the study by Jehkonen et al. (2000b), 38% of right hemisphere patients had visual neglect as evaluated by six BITC subtests within ten days of stroke onset. Neglect was defined as failure to reach the original cut-off score in at least two of the six conventional BIT subtests. Nijboer et al. (2013a) found evidence of visual neglect in 71% of right hemisphere stroke patients. In their study, neglect was defined based on the difference in the number of crossed letters in cancellation tasks on the left and right hand side; an asymmetry of at least two omissions was considered indicative of visual neglect. Ringman et al. (2004) reported visual neglect in 43% of right hemisphere stroke patients at the acute phase of stroke using NIHSS. In these studies (Jehkonen et al., 2000b; Nijboer et al., 2013a; Ringman et al., 2004) stroke patients did not receive thrombolytic treatment. The prevalence of visual neglect at the acute phase of stroke depends on the assessment method used (Azouvi et al., 2002, 2006; Bowen et al., 1999). However it is also possible that thrombolytic treatment administered within three hours of stroke onset might reduce the prevalence of visual neglect at the acute phase of stroke, as has been tentatively suggested in some earlier studies (e.g. Bugnicourt et al., 2008; Siekierka-Kleiser et al., 2006).

Mikulik et al. (2010) found that aphasia and neglect responded less well than other functions to thrombolytic treatment (as measured by NIHSS). Among patients with neglect, 6% without complete recanalization and 13% with complete recanalization recovered to normalized status (= no neglect) at two hours. Previously Felberg et al. (2002) found that 22% of stroke patients who had middle cerebral artery occlusion recovered, but higher cognitive functions (as manifested by aphasia) recovered later than sensation or motor function within 24 hours. Among patients with aphasia, 29% recovered completely, 57% recovered partly and 14% did not recover. The very first neurological deficit to recover after thrombolysis was gaze deviation (Felberg et al., 2002). In this Study (II), 15% of patients showed visual neglect post-thrombolysis, suggesting that these patients did not recover, although we were unable to establish whether they had visual neglect before thrombolysis. Nevertheless the results of this Study (II) showed that thrombolysis reduces the risk of visual neglect after right hemisphere stroke. The Felberg and colleagues (2002) suggest that early improvement is related to the immediate restoration of flow that occurs during thrombolysis infusion.

In the study by Meretoja, Strbian, Putaala, Kast, and Tatlisumak (2012), 52% of stroke patients with hemiplegia had visual neglect before receiving thrombolysis. Di Legge, Fang, Saposnik, and Hachinski (2005) reported similar findings. In their study, 46% of patients who received thrombolysis had visual neglect pre-treatment, whereas the figure for patients who did not receive thrombolysis was 15%. They found that the presence of visual neglect at pre-treatment positively predicted thrombolytic treatment within three hours of stroke onset. In this Study (II) we were not in the position to evaluate the presence of visual neglect using a standardized test battery before thrombolytic treatment because of the short time window for treatment (three hours), and therefore our results are not directly comparable with those presented in the recent literature. However, these results (Di Legge et al., 2005; Meretoja et al., 2012) indicate that the prevalence of visual neglect at pre-treatment is high.

Nys et al. (2006) found that thrombolysis had no effect on any cognitive domain during their six to ten-month follow-up. They assessed visual neglect using one cancellation task only. It is important to note that they did not take account of the multifactorial nature of the neglect syndrome. In other words thrombolysis may be effective in the treatment of some symptoms, but not necessarily others.

The present Study (II) showed that the presence of visual neglect was associated with the severity of stroke. Patients with visual neglect had more severe stroke than patients without visual neglect (Pedersen et al., 1997). Patients receiving thrombolytic treatment also had more severe strokes than untreated patients; this finding is again in line with previous results (Nys et al., 2006). Patients with more severe stroke tend to present faster at hospital (Adams et al., 2007). It should be emphasized that a large proportion of our patients had a low NIHSS score, which indicates that the majority of them had mild or moderate ischemic strokes. A low baseline NIHSS score and younger age has been shown to be a major clinical predictor of rapid neurological recovery (Machimpurath, Reddy, & Yan, 2010; Strbian et al., 2011).

From a methodological point of view, it is important to note that many previous studies have used NIHSS for purposes of evaluating visual neglect. It has been suggested (Hillis, Wityk, Barker, Ulatowski, & Jacobs, 2003) that the NIHSS score might provide an inaccurate estimate of visual neglect because it is not sensitive to right hemisphere cognitive functions. Seven out of the total of 42 possible NIHSS points are related to the measurement of language, while only two points are related to neglect. Woo et al. (1999) found that for a given NIHSS score, the median volume of right hemisphere strokes is consistently higher than the median volume of left hemisphere strokes. Di Legge et al. (2005) postulated that lack a standardized scores for the neglect syndrome may limit the access of patients with right hemisphere stroke to thrombolysis, and therefore patient selection to thrombolysis might be biased.

It is possible that our study, too, has problems with selection bias in that patients with the most severe disability could not be assessed with BITC. At least some of these were probably right hemisphere patients with severe stroke symptoms (NIHSS > 16) and with severe markers of visual neglect.

5.3 Rightward orienting bias after right hemisphere stroke

Several studies (e.g. Jalas et al., 2002; Mattingley et al., 1994; Samuelsson et al., 1996) have replicated the important finding that at baseline, rightward bias is more evident in visual neglect patients than in patients without visual neglect. This lends support to the assumption that an automatic orientation towards the right is an essential component of visual neglect (Gainotti et al., 1991; Karnath, 1988; Mattingley et al., 1994).

At follow-up, the intensity of rightward bias decreased in visual neglect patients compared to baseline, although this decrease was significant only in the line cancellation task. In patients without visual neglect, no such change was seen. The results for patients without visual neglect showed stronger left-sided lateralization than the results for visual neglect patients. This supports the assumption that residual attention problems are still present in patients with visual neglect, even though in our case almost all visual neglect patients improved during the follow-up as measured by BITC sum scores. These results are consistent with the model of recovery of speed (Karnath, 1988). Patients who tend to start cancellation tasks from the right hemispace also manage to search for targets on the left side using compensatory right-to-left visual strategies, and thus do not meet typical neglect criteria (left side omissions in cancellation tasks). The persistence of the first component would explain the residual deficits when right hemisphere stroke patients have regained some contralesional orienting abilities, such as managing to search targets on the left side (Karnath, 1988).

It has been suggested that a pseudo-random array stimulus sheet induces more visual rightward orienting bias than structured arrays (Jalas et al., 2002; Samuelsson et al., 1996; Weintraub & Mesulam, 1988). Samuelsson et al. (1996) suggested that the letter cancellation task might include cues that force patients to start the task from the left side. These habits may be closely related to language aspects and reading (Nicholls, Bradshaw, & Mattingley, 1999) since reading and writing are performed from left to right in most languages. As has been suggested earlier, we found in our study that a right-to-left strategy was uncommon in the letter cancellation task. Samuelsson et al. (1996) proposed that the star cancellation task does not present distinct clues that force the patient to start on the left or the right side of space. In this study star cancellation was the only task in which all the visual neglect patients showed a result at or below the cut-off score, confirming earlier results that star cancellation might be particularly sensitive to identifying visual neglect (Halligan et al., 1989; Jehkonen et al., 1998; Lindell et al., 2007). In the star cancellation task, almost half of the patients without visual neglect started from the right, suggesting that some patients who according to BITC scores do not have clear-cut visual neglect, may still suffer from a residual attention problem. Jalas et al. (2002) suggest that some right hemisphere stroke patients who do not develop clear-cut visual neglect may still suffer from rightward orienting bias, and caution is needed when interpreting rightward bias as a sign of pathological performance based on one type of cancellation task only.

It is possible that attention requirements vary between different cancellation tasks in this study. Sarri, Greenwood, Kalra and Driver (2009) suggested that the performance of neglect patients depends on the attentional requirements of the tasks. Our comparisons of these cancellation tasks showed that there were for instance different amounts of main stimuli and distractors (e.g. big stars in the star cancellation task), and that these stimuli were differently divided between the stimulus sheets (randomized and non-randomized arrays). Therefore, the results of different tasks are not fully comparable. It is quite possible that different stimulus sheets result in different cognitive loads (e.g. that the letter cancellation task activates different brain networks than the star cancellation task), and that different attentional resources are required. Using functional imaging, Fink et al. (2000) showed that line centre judgments activated the right parietal cortex, whereas square-centre judgments activated the lingual gyrus bilaterally, suggesting that different visual stimulus configurations evoke a different functional anatomy related to the performance of the specific spatial task. If these cancellation tasks load different resources of patients' attentional network, preference should be given to cancellation tasks with randomized arrays and without letters. It also is possible that visual rightward orienting bias might arise differently in different cancellation tasks, not only because of right hemisphere stroke but also because of ageing (Takio et al., 2009) and other confounding factors such as sleep deprivation (Manly, Dobler, Dodds, & George, 2005).

Recent experimental studies (Takio et al., 2009; Takio, Koivisto, Laukka, & Hämäläinen, 2011; Takio, Koivisto, Tuominen, Laukka, & Hämäläinen, 2012) with healthy participants found that tasks with a high cognitive load on spatial attention revealed only rightward spatial bias, independent of the nature of the stimuli in both the auditory and the visual modalities. Rightward biases were more common in children and in the old adult participants, suggesting that the spatial biases changed as a function of age. The authors (Takio et al., 2011, 2012) conclude that the decline seen in executive functions might also explain the overall decline in the performance of healthy older people. Manly et al. (2005) showed that a rightward shift in attention in healthy participants was associated with sleep deprivation. Therefore acute stroke patients may exhibit abnormal performance for a wide range of unspecific reasons related to their hospitalization, including new medications, fatigue and disrupted sleep. In our study, these factors were not systematically controlled, and therefore it is possible that these issues confound our results.

The present Study (III) involved some confounding background factors that need to be briefly discussed. Firstly, patients without visual neglect and healthy participants seemed to have a significantly longer education than patients with visual neglect. Azouvi et al. (2006) found that education and age had a significant effect on the performance of healthy controls in cancellation tasks: less educated and older participants had a greater number of omissions than those with a longer education or lower age. The difference between left and right omissions was also significantly associated with education: more left side omissions were associated with lower education, and more right side omissions with longer education (Azouvi et al., 2006). Ojala-Oksala et al. (2012) have recently suggested that in patients with stroke, a long educational history is associated with less post-stroke cognitive deficits in left and right hemisphere patients with mild or moderate ischemic stroke as evaluated three months post-stroke. Previously it has been suggested that length of education protects from brain injury through brain reserve capacity (Stern, 2002, 2009). The cognitive or brain reserve hypothesis states that high premorbid intelligence and education provide the subject with reserve capacity that compensates or buffers the brain against the effects of ageing and diseases (Stern, 2009; Valenzuela & Sachdev, 2006). It has also been suggested that higher age in stroke patients increases the odds of neglect as well as the severity of neglect (Gottesman et al., 2008; Linden et al., 2005; Ringman et al., 2004).

In the present Study (III) significant difference in age between the patient groups were not found, but our patients were quite aged. According to Gottesman et al. (2008), older right hemisphere stroke patients may have more brain atrophy, and may be less able to compensate for the consequences of cerebral infarction. Our results showed that patients without visual neglect had a longer education than patients with visual neglect. It is possible that patients without visual neglect had at baseline greater cognition resources as manifested by length of education than patients with visual neglect, and therefore had a stronger buffer or better compensation strategy for the avoidance of the various manifestations of visual neglect in cancellation tasks. As discussed above, it would be interesting to investigate the possible associations between orienting bias as well as age and education in stroke patients using different visual cancellation tasks.

The data from Study III provide only limited evidence regarding the association between rightward orienting bias and activities of daily living. Recently Nijboer, Van de Port, Schepers, Post and Visser-Meily (2013b) found that patients with neglect had significantly lower self-care, transfers and locomotion scores compared to patients without neglect. It has been suggested that right hemisphere stroke patients with and without visual neglect will often have more failures and accidents (Webster et al., 1995) and left sided collisions (Azouvi et al., 2002), or even have an increased risk of road accidents (Deouell et al., 2005).

Deouell et al. (2005) showed in a case report that several years after right hemisphere stroke, there was still an increased risk of traffic accidents. This patient had been involved in nine car accidents, all involving the left side of his car. According to the patient himself and his family members, he showed no signs of neglect in everyday life.

Following the last accident, the patient's BITC sum score was 143 points. However, a computerized task revealed a significant slowing of response to left-sided events as compared to right-sided events 12 years after stroke. Despite the high BITC sum score and individual and family reports, a mere rightward shift as measured by a computer-based assessment may limit the patient's daily activities and adversely affect his ability to work and drive, for instance (Deouell et al., 2005). Bonato (2012) suggests that deficits in awareness emerge in the contralateral hemispace when attentionally demanding computer tasks are performed and compensatory strategies cannot be implemented.

It is unknown whether mere rightward orienting bias after right hemisphere stroke as measured in paper-and-pencil cancellation tasks may lead to disabilities limiting patients' daily activities, ability to work (more demanding conditions) and driving. More detailed investigation is still needed to confirm our findings regarding demanding situations of everyday life, such as driving.

The present study confirmed previous findings that the right hemisphere has an elemental role in the orientation of attention (e.g. Heilman et al., 1980). Unfortunately, we were not in the position to analyse in more depth our brain imaging data and therefore to draw any conclusions relevant to the theory of attention network.

5.4 Visual orienting bias in patients with and without thrombolytic treatment and healthy controls

The data from Study IV confirm earlier findings that rightward orienting bias is a common phenomenon in patients with right hemisphere stroke, particularly in patients with visual neglect (Gainotti et al., 1991; Jalas et al., 2002; Mattingley et al., 1994), even after thrombolysis. To the best of the author's knowledge, there are no previous studies concerning the association between thrombolytic treatment and visual orientation bias following acute right hemisphere brain infarct, and therefore our results remain tentative.

Rightward bias is more common and severe in patients with pronounced signs of visual neglect (Webster et al., 1995). Therefore, in our study, the presence of visual neglect might partly explain why patients without thrombolytic treatment had more rightward bias than patients with thrombolytic treatment. When thrombolytic patients with and without visual neglect were compared, patients with visual neglect showed, predictably, more robust rightward bias than patients without visual neglect. When we compared the results between healthy controls and treated patients with and without visual neglect, the patient groups showed a clearer tendency, in fact in all cancellation tasks, to start on the right side of a given stimulus sheet than the healthy controls. Healthy subjects initially oriented towards the left (e.g. Pflughhaupt et al., 2004), irrespective of the task. Azouvi et al. (2006) found that approximately 80% of healthy controls used a left-to-right visual scanning strategy. In our study, 92% of healthy controls in the star cancellation task were left-biased. It has been suggested that this asymmetry results from dominant right hemisphere activation for spatial processing (Tant, Kuks, Kooijman, Cornelissen, & Brouwer, 2002).

The present findings suggest that the process of recovery from visual neglect and rightward bias at the acute phase of stroke in patients with or without thrombolytic treatment was incomplete. Compared with the results of healthy controls, rightward orienting bias was observed in three cancellation tasks in both patient groups. It seems that treatment within three hours of stroke onset might have some benefit in patients with first-ever right hemisphere stroke in terms of helping them use their cognitive resources, particularly when measuring attention bias in cancellation tasks. This might be related to the immediate restoration of flow that occurs during thrombolysis infusion, as Felberg et al. (2002) suggested.

It is important to note that our results do not answer questions about a possible causal relationship between orienting bias and thrombolytic treatment, as we were unable to examine our patients before thrombolysis.

5.5 Methodological evaluation and limitations

Any generalizations from the present results must be made with caution, and a few comments are also in order on the limitations of our studies. The articles reviewed included five studies by Paolucci and co-workers (1996, 1998, 2000, 2001a, 2001b) and two studies by Appelros et al. (2002, 2003). In latter the studies by Appleros et al. (2002, 2003), the patient samples were the same, while the participants for the studies by Paolucci et al. (1996, 1998, 2000, 2001a, 2001b) were drawn from a consecutive series of patients referred to a rehabilitation institution, thus representing a selected sample of stroke patients. Our review focused on the period between January 1996 and August 2005, which means that this sample is temporally limited and needs updating.

The number of patients included in the original studies was quite limited, and only right hemisphere stroke patients were evaluated. Another limitation of these studies has to do with patient selection, the sources of the lesion data, and the method used in assessing visual neglect. Unfortunately, some eligible stroke patients at the acute phase of stroke had to be excluded from the sample because our inclusion criteria required adequate cooperation in the clinical assessment. In addition, a few eligible patients on the neurological department were transferred to the rehabilitation centres or local hospitals before we had the time to ask them to participate in this study. A few patients refused to participate in the study, and some data had to be excluded because not all patients participated in the six-month follow-up. It is clear from all this that the results cannot be generalized to the whole stroke population, and these factors increase the risk of selection bias.

Unfortunately, the standardized BITC scoring system does not provide a quantitative assessment of lateralized bias. It is possible that some patients may miss items on the contralesional side of the test sheet, whereas others may miss the same number of targets but evenly across the sheet. The simple sum score number of omissions may be an ambiguous measure of visual neglect. Therefore, an analysis of starting points in cancellation tasks should provide useful information about visual neglect and about the process of visual neglect recovery. Furthermore our definition does not capture the heterogeneity of visual neglect, and therefore the results should be interpreted with caution. Only the peripersonal subtype of space was observed in this study.

For methodological reasons, we were unable to investigate patients' cognitive functions before treatment, and therefore we were not in the position to draw inferences about causal relationships, namely the direct effect of thrombolytic treatment on cognitive function. In addition, we did not have access to information about the exact time between thrombolytic treatment and first symptoms of stroke (onset-to-treatment time). Therefore, in future studies it would be interesting to investigate the association between time of onset-to-treatment and the presence of visual neglect, because early treatment is associated with better outcome (e.g. Marler et al., 2000; Strbian et al., 2011).

In our neuroradiological examinations, CT was completed as part of the patients' routine clinical care, but unfortunately CT did not allow for precise lesion localization or for the determination of lesion volume in some of our right hemisphere patients. Therefore we cannot exclude the possibility that the patient samples in our study had different lesion locations, which might have different manifestations of neglect (e.g. extrapersonal but not peripersonal neglect).

5.6 Practical implications and directions for future research

The results of this study have some important practical implications. Clinical examinations of right hemisphere stroke patients do not routinely include assessment of visual neglect. The assessment of visual neglect at the acute phase of stroke must rely on standardized methods. It is also important that further feasibility studies are conducted with a view to examining the subtyping of neglect symptoms. Although clinical screening methods are not yet available for the assessment of visual orienting bias in cancellation tasks, it makes sense to systematically determine patients' orienting bias (i.e. left or right as manifested by starting points) in cancellation tasks. In clinical contexts it should be easy to include an assessment of orienting bias in BITC tests. It would also be necessary to add a time limit to cancellation tasks because making a task more resource demanding will increase its sensitivity to detecting neglect (Barrett et al., 2006). All this would provide important additional information about the visual neglect recovery process.

Future studies should aim to establish the presence of visual neglect not only after, but also before thrombolysis using sensitive cancellation tasks (e.g. star cancellation task). This, however might be difficult because of the short time window from onset to treatment at the acute phase of stroke. In other words, due to the small group sizes and the absence of long-term follow-up opportunities, there is pressing need for well-designed and high quality research, particularly for randomized controlled trials, examining the effect of thrombolysis on cognitive functioning at the acute phase of stroke, as well as for follow-ups with larger patient groups including left hemisphere stroke patients so that useful generalizations can be drawn.

In our studies we have used only paper-and-pencil tasks to identify the presence of visual neglect. These tasks are in widespread clinical use and easy to apply, but they may be less sensitive than computerized tests for detecting residual (but probably still disabling in patient's everyday life) symptoms of visual neglect (i.e. Bonato et al., 2012;

Deouell et al., 2005). Therefore, future studies should include some simple computerized tasks, such as reaction time tasks to detect residual attention difficulties (which can affect the person’s ability to drive, for instance).

Finally, because we were unable to analyse our CT data in detail, associations between visual orienting bias and lesion location as measured by magnetic resonance imaging or diffusion tensor imaging could also be an interesting topic for future research.

6. SUMMARY AND CONCLUSIONS

The following conclusions can be drawn from the results of Studies I-IV:

a) The review of earlier research revealed differences in the accuracy of the methods used to assess neglect, in the timing of assessments, and in patient selection procedures. The reported prevalence of visual neglect is probably influenced by the range of assessment methods used.

b) The prevalence of visual neglect after thrombolytic treatment was 15%. Thrombolytic treatment administered within three hours of stroke onset independently predicted absence of visual neglect at the acute phase of stroke.

c) Visual neglect patients showed a stronger rightward bias than patients without visual neglect at the acute phase of stroke. The intensity of orienting bias and the presence of visual neglect changed as a function of time. After six months of recovery, visual neglect was likely to be improved as measured by BITC, but signs of rightward orienting bias were still detected, suggesting that recovery from visual neglect was incomplete.

d) Rightward orienting bias was observed in all patient groups, but it was more common in patients without thrombolysis. Even though they received thrombolysis, patients with and without visual neglect showed more signs of orienting bias than the healthy participants, suggesting that the recovery process was incomplete.

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