Visuospatial Neglect and Processing Speed: Importance of Lateralized and Nonlateralized Symptoms as Predictors of Functional Outcome after Stroke

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To Angelica,
Axel and Lova

Abstract

Viken, J. I. (2013). *Visuospatial neglect and processing speed: importance of lateralized and nonlateralized symptoms as predictors of functional outcome after stroke.* Department of Psychology and the Stroke Research Group at the Department of Neuroscience and Physiology, University of Gothenburg, Sweden.

Visuospatial neglect (VSN) is a disorder that is commonly observed in the acute phase after stroke, especially following right hemisphere damages. Patients who have VSN exhibit impaired awareness and responses to visual stimuli located towards the side opposite the brain lesion (contralesional side). Previous studies have shown that the presence of VSN is a predictor of functional dependency following stroke. The present paper investigated how different sub-symptoms of VSN are related to recovery from VSN and later functional outcome. The sub-symptoms of VSN were assessed in an early stage after stroke (baseline ~7 days) and in a follow-up at about three months using standard paper and pencil tests of cancellation and visual search. Neurological deficits were examined with the Scandinavian Stroke Scale within the first week and about three months after stroke. Functional dependency was measured with the modified Rankin Scale at a three month (Studies I- III), two year (Study II) and 7 year (Study IV) follow-up and scores of ≤2 were classified as functional dependency. The Frenchay Activities Index was used to assess level of activity at 7 years post stroke (Study IV). Patients in the current studies were sub-samples from the prospective Sahlgrenska Academy Study on Ischemic Stroke (SAHLSIS).

Study I included 375 consecutive stroke patients who were divided into three groups having lateralized-, nonlateralized-, or no visual inattention. The study examined the course of lateralized and nonlateralized symptoms of inattention across time in relation to functional outcome and neurological symptoms. Compared to the other two groups, participants with lateralized inattention exhibited significantly more severe neurological symptoms, functional dependency and persisting visual inattention, both at baseline and after three months. Stepwise logistic regressions revealed that lateralized inattention at baseline was an important and independent predictor of functional dependency following right hemisphere damage, but not after left hemisphere damage.

In **Study II** a consecutive series of 105 patients with right hemisphere stroke was included. The relative importance of sub-symptoms of VSN as predictors of functional dependency was investigated. Three sub-symptoms of visuospatial neglect (the total number of omissions, asymmetry of omissions, and right capture of attention in orientation) and two symptoms related to VSN (visual processing speed and repetitive identification of previously detected targets) were analyzed as predictors of functional dependency. The univariate analyses showed that right capture of attention in orientation, asymmetry of omissions and slowed processing speed all had strong and significant associations with functional dependency at three months and at two years after stroke. Moreover, stepwise logistic regressions identified right capture of attention as the only significant predictor of dependency at three months whilst slowed processing speed was the only significant predictor of dependency at two years.

In **Study III** the same right hemisphere patients as in Study II were included. The aims were to investigate the pattern of change in the sub-symptoms of VSN and processing speed from baseline to the three month follow-up, and to explore the concurrent associations at three months between the classification of functional dependency and the sub-symptoms of VSN and processing speed. For pattern of change in VSN symptoms, the results indicated that the patients with VSN at baseline had less improvement in the measures of right capture of attention and asymmetry of omissions than in processing speed and omissions. At three months, the most important correlates with functional dependency were processing speed and right capture of attention in orientation.

Study IV examined the relative importance of symptoms of VSN and symptoms related to VSN as predictors of functional dependency and activity level at 7 years in 57 right hemisphere stroke patients. Multivariate logistic regression and partial correlations identified deficits in processing speed at baseline as the most important predictor of long term outcome regarding dependency and activity level. This was true also after controlling for overall stroke severity at baseline and year of education at the time of the follow-up.

Conclusions: The results show that assessing sub-symptoms of VSN and symptoms related to VSN at an early phase after a right hemisphere stroke can provide relevant prognostic information regarding long-term outcome. Overall, processing speed at baseline was found to be the most important predictor of later outcome, and processing speed was also the symptom associated with VSN that showed the least improvement from baseline to the three month follow-up.

Keywords: Functional outcome; Neglect; Recovery; Stroke; Visual inattention; Visual search, Processing Speed

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LIST OF PAPERS

This thesis is based on the following four papers, referred to in the text by their roman numerals:

I. Viken, J. I., Samuelsson, H., Jern, C., Jood, K., & Blomstrand, C. (2012). The prediction of functional dependency by lateralized and non-lateralized neglect in a large prospective stroke sample. *European Journal of Neurology, 19*, 128-134.

II. Viken, J. I., Jood, K., Jern, C., Blomstrand, C., & Samuelsson, H. Ipsilesional bias and processing speed are important predictors of functional dependency in the neglect phenomenon after a right hemisphere stroke. Manuscript submitted for publication.

III. Viken, J. I., Jood, K., Jern, C., Blomstrand, C., & Samuelsson, H. Post-acute neglect symptoms: recovery and the relationship with neglect- and functional outcome at three months post-stroke. Manuscript unpublished.

IV. Viken, J. I., Jood, K., Jern, C., Redfors, P., Holmegaard, L., Blomstrand, C., & Samuelsson, H. Processing speed and symptoms of neglect as predictors of long-term outcome after right-hemisphere stroke. Manuscript unpublished.

SVENSK SAMMANFATTNING

Visuospatial neglekt (VSN) är ett vanligt syndrom efter stroke (slaganfall), särskilt efter en skada inom den högra hjärnhalvan. Det innebär att personen får nedsatt medvetenhet om det hon ser (visuella stimuli) på motsatt sida i förhållande till hjärnskadans läge och visar nedsatt förmåga att aktivera rörelser mot dessa stimuli. Dessa funktionsbegränsningar kan ses även då primär sensorisk och motorisk funktion verkar intakt. Visuospatial neglekt är ett heterogent fenomen med olika uttryck som kan uppträda var för sig eller i olika kombinationer. En patient med VSN kan exempelvis uppvisa neglekt för stimuli som befinner sig inom räckhåll, men inte för stimuli som befinner sig på längre avstånd, utom räckhåll. De fyra delstudier som beskrivs i detta arbete baseras på studier av neglektsymtom för stimuli som finns inom patienternas räckhåll.

De förändringar i beteendet som är karakteristiska för VSN kan delas upp i några basala delsymtom som tillsammans troligen utgör kärnan i detta fenomen. Tre sådana delsymtom är 1) en inledande spontan orientering av den visuella uppmärksamheten mot stimuli långt ut på samma sida som hjärnskadan, 2) en visuell ouppmärksamhet dvs. att viktiga stimuli inte uppmärksammas, och 3) en asymmetri i denna ouppmärksamhet vilket innebär att antal missade stimuli ökar i motsatt riktning i förhållande till skadans läge – vid en högersidig skada ökar alltså antal missar åt vänster sida. I samband med VSN ses ofta också andra mer generella begränsningar, såsom 1) en generellt nedsatt kapacitet att processa information vilket kan visa sig i form av generell sänkning av processhastighet och 2) ett nedsatt visuospatialt arbetsminne vilket kan leda till upprepad identifikation av redan uppmärksammade målstimuli vid en visuell avsökningsuppgift.

Tidigare studier har visat att förekomst av VSN i det tidiga skedet efter insjuknandet kan förutsäga hur aktiva eller hjälpberoende patienterna blir i dagliga funktioner och aktiviteter längre fram under återhämtningen. De flesta av dessa studier har dock inte gjort någon åtskillnad mellan betydelsen av olika basala delsymtom av det slag som beskrivits ovan. Det saknas studier av den relativa betydelsen av de olika kärnsymtomen och nära relaterade symtom vid VSN när det gäller självständighet och aktivitetsnivå i dagliga aktiviteter och social funktion. Det första delarbetet i denna avhandling fokuserar på betydelsen av asymmetrisk kontra icke-asymmetrisk nedsättning i uppmärksamheten. De resterande tre delstudierna innebär fördjupade studier av de kärnsymtom som beskrivits ovan. Dessa fenomens betydelse analyseras i förhållande till hjälpberoende och aktivitetsnivå. Det övergripande syftet med

denna avhandling har varit att studera om en enkel undersökning i akutskedet på sjukhuset kan ge vägledning att förutse fortsatta förloppet och därmed behov av rehabiliterande insatser och stöd.

I det tidiga skedet (cirka 7 dagar efter strokeinsjuknandet) och vid en uppföljning cirka tre månader efter stroke undersöks VSN och relaterade symtom med standardiserade papper-och-penna test av visuell avsökning och identifikation av målstimuli. Dessutom undersöks olika neurologiska symtom med ”Scandinavian Stroke Scale” (SSS). Funktionsnedsättning och hjälpberoende undersöks med ”the modified Rankin Scale” (mRS) och ”the Frenchay Activities Index” (FAI). Ett resultat ≤ 2 i mRS klassificerades som att patienten fortfarande har ett hjälpbehov i sina dagliga funktioner; undersökt vid tre månader (Studier I - III), två år (Studie II), och 7 år (Studie IV) efter strokeinsjukandet. FAI användes för att identifiera patienternas aktivitetsnivå 7 år efter stroke (Studie IV). Patienterna som ingår i studierna utgör subgrupper från den större prospektiva studien ”Sahlgrenska Academy Study on Ischemic Stroke” (SAHLSIS).

Studie I omfattar en konsekutiv serie av 375 stroke patienter som delades in i följande tre grupper: lateral asymmetrisk ouppmärksamhet, icke-asymmetrisk ouppmärksamhet och ingen ouppmärksamhet. I studien undersöktes förekomst och förändring över tid av asymmetrisk ouppmärksamhet och av icke-asymmetrisk ouppmärksamhet och dessa fenomens relation till hjälpbehov och neurologiska symtom. Jämfört med de övriga två grupperna hade gruppen med asymmetrisk ouppmärksamhet signifikant svårare neurologiska symtom, mer behov av hjälp och mer kvarstående visuell ouppmärksamhet, både direkt efter och tre månader efter det akuta insjuknandet. En analys av materialet med stegvis logistisk regression identifierade asymmetrisk ouppmärksamhet som en viktig och oberoende prediktor av hjälpberoende efter stroke inom höger hjärnhalva, men inte efter en vänstersidig stroke.

I **Studie II** inkluderades en konsekutiv serie av 105 patienter med stroke inom den högra hjärnhalvan. I denna studie undersöktes den relativa betydelsen av olika basala delsymtom som är relaterade till VSN. Dels undersöktes de tre fenomen som utgör kärnsymtom vid VSN (inledande spontan lateral orientering av uppmärksamheten, totalt antal missade stimuli och grad av asymmetri i dessa missars position) och dels undersöktes två symtom som är relaterade till förekomst av VSN (nedsatt hastighet i processande av visuell information och upprepad identifikation/uppläsning av samma målstimulus). En inledande univariat analys visade att följande tre fenomen hade ett starkt och signifikant samband med ökat hjälpberoende såväl vid tre månader som vid två år efter insjuknandet: inledande spontan lateral orientering av uppmärksamheten, grad av asymmetri i uppvisad ouppmärksamhet och nedsatt hastighet i processande av den visuella informationen. En efterföljande analys med stegvis logistisk regressionsanalys identifierade 1) en inledande spontan lateral orientering av uppmärksamheten som den enda signifikanta prediktorn av hjälpberoende tre månader efter insjuknandet och 2) nedsatt hastighet i processande av visuell information som den enda signifikanta prediktorn av hjälpberoende två år efter insjuknandet.

Studie III omfattade samma urval av patienter som i Studie II. Syften med denna studie var att undersöka hur uttrycket av delsymtomen relaterade till VSN ändrar sig från det tidiga skedet till uppföljningen vid tre månader. I denna studie analyserades också den relativa styrkan av korrelationerna mellan hjälpberoende vid tre månader och de olika symtomen av VSN vid samma tidpunkt. När det gäller förändringen i symptomen relaterade till VSN, visade resultaten att återhämtning från en spontan lateral orientering av uppmärksamheten och asymmetriska missar var bättre än återhämtning från totalt antal missar och processhastighet. Stegvis logistisk regressionsanalys visar också signifikanta korrelat mellan hjälpberoende och spontan lateral orientering av uppmärksamheten samt mellan hjälpberoende och processhastighet.

Studie IV undersökte den relativa betydelse av de olika akuta delsymtomen relaterade till VSN när det gäller prediktion av hjälpberoende och aktivitetsnivå efter 7 år. Femtiosju patienter med strokeskadan i högra hjärnhalvan undersöktes. Stegvis logistisk regressionsanalys identifierade processhastighet i det akuta skedet som den viktigaste prediktorn för hjälpberoende och aktivitetsnivå 7 år efter stroke.

Studierna har visat att relativt enkla papper-och-penna test som används i det akuta skedet efter stroke kan ge information som är relevant för bedömningar av senare prognos. Sådan information kan vara till stöd vid planeringen av framtida behov av stödinsatser eller rehabilitering. Det prognostiska värdet kan ökas genom att lägga till några få specifika mått. Ett sådant mått är en registrering av den initiala orienteringen av uppmärksamheten i uppgiften (var avsökningen påbörjas) och om patienterna missar relevanta stimuli på motsatt sida av uppgiften. Genom införande av sådana registreringar kan känsligheten för identifiering av neglekt öka. Sådant beteende i testen kan indikera att patienten får ökad risk att möta svårigheter i sina dagliga göromål i ett senare skede. Dessa tecken är viktiga att registrera tidigt efter stroke då de kan vara svåra att identifiera senare på grund av relativt snabb återhämtning av de manifesta asymmetriska symtomen. Kopplingen till risk för hjälpberoende verkar dock bestå även om symptomen förbättras.

Ett andra mått som är värdefullt att inkludera är en registrering av tiden patienterna använder för att genomföra ett visuellt överstrykningstest. Studierna som presenterats här visar att detta mått gav den viktigaste prognostiska informationen angående risk för hjälpberoende sju år efter en stroke. Processhastighet i det akuta skedet kunde exempelvis skilja patienter som rapporterade en inaktivitet i dagliga aktiviteter från patienter med en hög aktivitetsnivå.

Som en följd av kriterierna för inkludering i dessa studier är resultaten begränsade till att gälla patienter med högersidig hjärnskada och patienter under 70 år. Resultaten visar att sänkt visuell processhastighet är en viktig komponent att fokusera på när man vill predicera funktionell aktivitetsnivå i ett längre perspektiv.

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CONTENTS

BACKGROUND AND INTRODUCTION

Neglect is a complex disorder commonly observed in the acute phase after a stroke. Patients suffering from neglect demonstrate an inability to detect and respond to stimuli located on the opposite side of their lesion (contralesional), even when primary sensory and motor functions are intact (Halligan & Marshall, 1993, 1998). It is as if the contralesional side does not exist at all for some of these patients (Halligan & Marshall, 1998). Thus, neglect is an asymmetric disorder in which patients' performance become more impaired towards the contralesional side.

The research reviewed in this introduction will show that patients with neglect following a stroke tend to have more severe neurological handicap, and slower and less efficient rehabilitation compared to stroke patients without neglect. To have neglect also predicts an inferior functional outcome in the future. Recent theorizing as to the mechanisms of neglect has suggested that a combination of deficits in some components might constitute the clinically observed symptoms of neglect. Little is currently known with regard to the relative importance of the symptoms related to these different components in predicting later outcome in activities of daily living and for the pattern of recovery from neglect.

The main objective of the current thesis is to explore if different symptoms associated with neglect, when assessed with basic clinical tests at the early post-acute phase after stroke, can refine prediction of the patients reported need for help in daily activities for up to 7 years after stroke. When the term "post-acute" is used in order to describe the time for the assessments conducted in the four papers in this thesis, it simply means the early time after the first day or days of acute illness. It typically signifies the first week after the stroke onset, or in unstable patients with severe illness, the first weeks after the stroke. That is, a time when the patient is in acute care at an acute stroke unit.

Different Sub-types of Neglect

Several sub-types of neglect, which can occur in combination or separately, have been identified (Buxbaum et al., 2004; Heilman, Watson, & Valenstein, 1993; Kerkhoff, 2001; Stone, Halligan, Marshall, & Greenwood, 1998). Various terms have been used to denote these different sub-types.

The term personal neglect is used when patients fail to attend toward the contralesional side of their body. Patients with personal neglect often do not dress, comb or groom their affected side. Also, they might not detect tactile stimuli on the contralesional side of their body, especially when such tactile stimulation is applied simultaneously on both sides of the body (tactile extinction).

Motor neglect refers to an impairment in which the patient is aware of a stimulus but nevertheless fails to move the contralesional arm in response to the stimulus, for instance, the patient might see a ball coming towards her but, in spite of her intention to do so, she fails to move her arm to catch the ball (Heilman et al., 1993).

In representational neglect (Bisiach, Luzzatti, & Perani, 1979) the patient shows an impaired representation of space leading to an inability to adequately scan or create representations of familiar scenes which are retrieved from memory. For example, a patient with representational neglect is asked to imagine the map of southern Sweden seen from Malmö and to recall as many cities as she can. The patient will mention cities located to the side of the map ipsilesional to her brain-damage (e.g., Karlskrona and Kalmar), ignoring cities located to her contralesional side (e.g., Halmstad and Göteborg). Then, if the patient is asked to imagine the same map from the vantage point of Borlänge, the previously ignored cities (now on her ipsilesional side) are identified whilst previously mentioned cities (now on her contralesional side) are ignored.

Spatial neglect is related to impairments in responding to and processing of external stimuli in space. This type of neglect can affect more than one modality. Patients might fail to report auditory or visual stimuli, or both (Buxbaum et al., 2004; Stone et al., 1998). That is, patients do not detect objects and persons in the contralesional side or sounds coming from this side. Neglect in the visual modality (visuospatial neglect or VSN) is more frequent and severe than auditory or tactile neglect (Gainotti, 2010). The studies presented in this paper are related to visuospatial neglect.

Visuospatial Neglect

It is difficult to derive a reliable frequency rate of neglect from the literature due to methodological differences, such as subject selection and type and timing of assessments (Bowen, McKenna, & Tallis, 1999). These differences in methodology have resulted in a large variability in the observed occurrence rates of neglect. The frequency rates following right brain-damage (RBD) have been found to range from 12% to 100%, and following left brain-damage (LBD) the rates ranged from 0% to 76% (Bowen et al.). However, in three recent studies with large samples (Appelros, Karlsson, Seiger, & Nydevik, 2002; Pedersen, Jørgensen, Nakayama, Raaschou, & Olsen, 1997; Ringman, Saver, Woolson, Clarke, & Adams, 2004), of which two were community based (Appelros et al.; Pedersen et al.), the observed frequency rate of visuospatial neglect in post-acute stroke patients was 20-23%.

The incidence of VSN at a late stage after stroke (from three months after onset) also varies with reported frequencies of 2 - 50% in RBD and 0 - 19% in LBD (Black et al., 1995; Kotila, Niemi, & Laaksonen, 1986; Stone, Wilson, et al., 1991; Sunderland, Wade, & Langton-Hewer, 1987; Wade, Wood, & Langton-Hewer, 1988). In a relatively large stroke register study on patients with a first ever stroke (*n* = 197), Sunderland and colleagues observed neglect in 2% of RBD and in none of LBD patients six months after stroke. In a prospective cohort study (*n* = 294) Black and coworkers found that 17.1% of RBD and 10% of LBD patients had neglect three months post stroke. All of these studies of neglect at later stages had various methodological drawbacks of the same kind as those described by Bowen et al. (1999). In the study by Sunderland and colleagues the measures used to classify visuospatial neglect probably had low sensitivity and in the study by Black and coworkers the number of participants who were unable to undergo assessment was high (35.1%). There is a lack of community based large studies which describe the frequency rate of VSN at a late stage (three months or more) after stroke.

Several studies have shown that visuospatial neglect is more frequent and more severe following RBD compared to LBD (Bowen et al., 1999; Fullerton, McSherry, & Stout, 1986; Heilman et al., 1993; Ringman et al., 2004; Stone, Halligan, & Greenwood, 1993). In a recent study, using a novel continuous measure of VSN severity based on “Center of Cancellation” (CoC; Rorden & Karnath, 2010), Suchan, Rorden, and Karnath (2012) found that VSN was less frequent following LBD but, when present, the severity of VSN after LBD was similar to that following RBD.

The area of the brain most often related to VSN is the right temporo-parietal junction and adjacent regions, such as the superior temporal lobe, the inferior parietal lobe and the subcortical white matter in this part of the brain (Golay, Schnider, & Ptak, 2008; Karnath, Fruhmann-Berger, Kuker, & Rorden, 2004; Samuelsson, Jensen, Ekholm, Naver, & Blomstrand, 1997; Vallar, 2001; Verdon, Schwartz, Lövblad, Hauert, & Vuilleumier, 2010). Prefrontal regions have also been linked to VSN (Vallar; Verdon et al.). Also, albeit less frequent, damages to subcortical gray matter such as the basal ganglia and thalamus can produce VSN (Karnath, Himmelbach, & Rorden, 2002). A large lesion, including several of the critical areas described above, is associated with more severe symptoms of VSN (Egelko et al. 1988; Kertz & Dobrowolski, 1981; Levine, Warach, Benowitz, & Calvanio, 1986). The current studies only discuss localization of damages in relation to the right or left hemispheres and to the brainstem and the right or left cerebellum.

VSN is a heterogeneous disorder and several sub-types which can occur in combination or separately have been identified (Buxbaum et al., 2004; Gainotti, 2010; Heilman et al., 1993; Kerkhoff, 2001). Visuospatial neglect might be described in relation to different reference frames. In egocentric or body-centered neglect patients omit stimuli located contralesional to the subjective mid-line of their body or to specific parts of the body, for instance, the patient fail to pick up those cookies on a baking-tray that are located contralesional to his or her body midline. Object-centered or allocentric neglect defines the phenomenon in which the contralesional part of objects is omitted, regardless of the objects location in relation to the body. Another categorization of VSN is extrapersonal and peripersonal, patients with extrapersonal neglect fail to detect stimuli in far space whilst patients with peripersonal neglect omit stimuli in near space within reach (Cowey, Small, & Ellis, 1994; Halligan & Marshall, 1991).

Studies have also shown that there might be a motor component in VSN in addition to the perceptual-attentional impairments (Husain, Mattingley, Rorden, Kennard, & Driver, 2000; Mattingley, Phillips, & Bradshaw, 1994; Milner, Harvey, Roberts, & Forster, 1993). That is, patients with VSN might exhibit a delayed initiation and slow movements in tasks requiring an action towards the side of space opposite to the brain-damage.

The current studies focus on peripersonal neglect and on neglect symptoms exhibited in relation to the body mid-line (i.e. in an egocentric reference frame), but do not try to differentiate between body- and object centered symptoms, nor between motor and attentional components. The remaining part of the background will focus on subjects that are more specifically related to the aims of the papers in the present thesis.

SPECIFIC BACKGROUND

Components of VSN

The asymmetric impairment exhibited by patients with VSN is probably related to deficits in a set of “core” components (Corbetta & Shulman, 2011; Parton, Malhotra, & Husain, 2004). In this dissertation the term “core” is related to components suggested to be essential in producing the clinically observable VSN syndrome. VSN can then be the result of a combination of deficits in the proposed core components. These deficits are thought to cause symptoms of impairment in both lateralized (spatial asymmetry) and nonlateralized (no spatial asymmetry) visual attentional performance.

At least three symptoms of the tentative core components can be identified in conventional clinical tests of VSN. A nonlateralized symptom is when patients with VSN exhibit general visual inattention; i.e. they fail to detect targets and objects in the surrounding space. In paper-and-pencil tests such inattention means that patients with VSN make more target omissions than patients without neglect (Stone, Halligan, Wilson, Greenwood, & Marshall, 1991). One lateralized symptom of VSN is an asymmetry in these target omissions. The most favorable performance is typically observed at the outermost ipsilesional side and the number of omissions increases towards the contralesional side (Heilman et al., 1993). Another lateralized symptom of the possible core components is an initial spontaneous right capture of orientation in attention (ipsilesional bias). That is, the patient’s attention is automatically drawn towards the extreme right side when asked to perform a visual search (Gainotti, 2010; Kinsbourne, 1993; Samuelsson, Hjelmquist, Naver, & Blomstrand, 1996). For instance, when asked to cross out targets on a test sheet, a patient with VSN often begins the cancellations towards the outermost right targets. Patients with severe symptoms of VSN may only mark a few of the rightmost targets and then express that they are finished with the task. Other patients are able to work their way “backwards” toward the left sided targets, however, these patients still tend to omit some targets on the left side of the sheet.

Thus, at least one nonlateralized (general visual inattention) and two lateralized (asymmetry of inattention and ipsilesional bias) symptoms of the tentative core VSN deficits can be assessed in the conventional clinical tests of VSN.

Impairments and Disorders Related to VSN

Besides the lateralized and nonlateralized components thought to be core to the VSN syndrome, several different impairments and disorders related to the VSN phenomenon have been identified. Patients suffering from VSN usually have more severe overall neurological impairments than patients without VSN (Paolucci, Antonucci, Grasso, & Pizzamiglio, 2001) and visuospatial neglect tends to co-exist with visual field deficits (Cassidy, Bruce, Lewis, & Gray, 1999). Studies have also shown that impairments in spatial working memory, the ability to keep objects and their localization in space maintained in memory for short periods of time, might be related to VSN (Husain et al., 2001; Wojciulik, Husain, Clarke, & Driver, 2001). In two case studies on neglect these authors found repeated re-fixations of right-sided locations, and re-cancellations of targets which were previously identified and marked with invisible ink. Also, the neglect was found to be more severe when the patient was using invisible ink compared to visible cancellations. The authors thus suggested that impaired spatial working memory may exacerbate the clinical expression of VSN.

Nonlateralized attentional components have also been related to visuospatial neglect such as impaired sustained attention and slow visual processing speed, as well as specific attentional attributes of tests, such as stimulus salience and overall attentional load (Aglioti, Smania, Barbieri, & Corbetta, 1997; Karnath, 1988; Robertson, 1993; Robertson & Frasca, 1992; Samuelsson, Hjelmquist, Jensen, Ekholm, & Blomstrand, 1998). Even though such attentional components and impairments often are found in relation to VSN, they may also be observed without typical asymmetric symptoms of neglect. Two nonlateralized symptoms of impairment related to VSN, which can be assessed by conventional clinical VSN tests, are visual processing speed and repeated identifications of the same targets.

Assessment of VSN

A large number of bedside paper-and–pencil tests (e.g., copying and free hand drawings, bisecting lines of different lengths, and visual searches with identification and cancellation of targets) have been used clinically and in research to assess prevalence, severity, and recovery of VSN after stroke. Such conventional tests tend to require relatively short time to administer and are often easily understood by patients, making these tests suitable for use shortly after the acute stage of a stroke. The literature on VSN tests has highlighted that, due to varying sensitivity of individual test, a set of different tests provide better sensitivity in assessing VSN (e.g., Azouvi et al., 2006, 2002; Halligan, Marshall, & Wade, 1989; Jehkonen, 2002).

In tests of VSN, like in the standardized conventional part of the Behavioral Inattention Test (BIT; Stone, Wilson, et al., 1991; Wilson, Cockburn, & Halligan, 1987), occurrence and severity of VSN have often been based upon the total number of target omissions. Scoring only the number of omissions does not directly assess any lateralized gradient in impaired visual attention. Thus, different ways of indicating the severity or the left- to right-sided ratios of lateralized inattention have been utilized (e.g., Friedman, 1992; Fullerton et al., 1986; van Kessel, van Nes, Brouwer, Geurts, & Fasotti, 2010). However, such measures do not tend to be reliable indicators of VSN severity (Rorden & Karnath, 2010). To provide a better assessment of VSN severity, Rorden and Karnath developed software which can be used to calculate an index of "Center of Cancellation" (CoC) in any cancellation task. In short, this index is based upon the calculation of the mean horizontal position of all detected targets and provides a normalized center of mass index ranging from -1 to +1. Thus, symmetrical performances will produce scores close to 0 whilst strongly asymmetrical scores will produce scores close to +1 (identifying targets only at the outer right side of the test) or -1 (identifying targets only at the outer left side of the test).

To assess the sensitivity of omissions and asymmetry of omissions in detecting VSN, van Kessel and colleagues (2010) tested 45 stroke patients (right and left hemisphere damaged, age range = 34-80 years), recruited at a rehabilitation center two to 9 weeks post stroke onset, with a battery of conventional and computerized tests of VSN. In the total patient sample the authors found that a ratio score of asymmetry in omissions could distinguish better between neglect and non-neglect patients than omissions only. For the right hemisphere damaged patients it was found that omissions and asymmetry of omissions produced the same results in detecting neglect, suggesting that computing asymmetry in omissions in this group of stroke patients did not refine the assessment of neglect. However, by using asymmetry scores of the reaction times from the left and right side (target presented left, right, or centrally on a large screen), more patients were identified as having neglect.

Samuelsson, Hjelmquist, Naver, and Blomstrand (1995) investigated the accuracy of identifying VSN in 60 consecutive right hemisphere patients (mean age = 60.25 years, *SD* = 12.58, range = 21-77) one to 8 weeks after stroke. The authors used 7 subtests of the BIT battery and compared the frequencies of patients identified as having VSN based on (1) having at least one of the subtests at or below the cut-off for omissions, (2) being at or below cut-off for the aggregated cut-off for omissions based on all 7 tests, or (3) a score at or below cut-off for omissions in at least one test and a lateralization in the performance. The three criteria identified different total numbers of patients as having VSN. One result from this study was that utilizing the combination of omissions and lateralization of performance, more patients were identified as having VSN than when using only the aggregated cut-off across the 7 subtests. The fact that the studies by van Kessel et al. (2010) and Samuelsson et al. show different accuracy in identifying patients with VSN by using a measure of asymmetry in omissions might be due to the differences in calculating and setting cut-offs for VSN.

Ipsilesional bias has also been assessed in conventional tests of VSN (Azouvi et al., 2006, 2002; Jalas, Lindell, Brunila, Tenovuo, & Hämäläinen, 2002; Kettunen, Nurmi, Dastidar, & Jehkonen, 2012; Nurmi et al., 2010; Samuelsson et al., 1996). Overall, these studies found that occurrence of ipsilesional bias are tightly associated with having VSN. However, even patients without VSN, as measured with the conventional tests, could exhibit an ipsilesional start in visual searches for targets. Ipsilesional bias without omissions and/or lateralization of omissions might be an indication of sub-clinical or residual VSN (Kettunen et al., 2012; Samuelsson et al., 1996).

As for the sensitivity in detecting VSN, studies have suggested that cancellation tests are amongst the best individual tests. For instance, Halligan and colleagues (1989) assessed stroke patients in a rehabilitation unit at about 3 months post-stroke with the BIT. These authors found that the Star Cancellation sub-test of this battery identified the same patients as having neglect as the aggregated score from all the tests of the BIT. Lindell and coworkers (2007) assessed patients at about two weeks after a right hemisphere stroke with different clinical measures of neglect. This study found that the Star Cancellation test was amongst the best individual test for detecting VSN.

Rengachary, d'Avossa, Sapir, Shulman, and Corbetta (2009) assessed clinically diagnosed left hemi-space neglect patients (*n* = 30), as diagnosed by a physician or an occupational therapist at two weeks after stroke, with a battery of commonly used tests of VSN and computerized reaction time tasks (Posner cueing reaction time paradigm). The patients were recruited at a rehabilitation unit and were assessed approximately two weeks and 9 months after stroke. Large variations were found between the different tests with regard to accuracy in differentiating between neglect patients and healthy controls. In the clinical tests used in this study, all were better than chance in identifying neglect at two weeks, with the total number of omissions showing a strong tendency of being a better indicator of neglect than left-right difference scores. Also, the tests were markedly worse at identifying occurrence of baseline neglect when administered at about 9 months after the stroke compared to the concurrent assessment at two weeks. However, at the 9 months assessments, the Posner left-to-right reaction time index was significantly better at identifying baseline neglect compared to paper-and-pencil tests. Both at two weeks and 9 months after stroke the Posner left-to-right index was the best test for identifying neglect at the two week baseline. Overall, several of the clinical tests were found to have moderate accuracy in detecting neglect at two weeks, but the reaction time measure was found to be the best test, especially at the later stage after stroke. The authors concluded that most of the clinical tests have acceptable sensitivity in detecting neglect in the early phases after stroke, but are less sensitive at the later stages. It should be noted that neglect was clinically diagnosed by a physician or a therapist only at baseline and not at the follow-up. Thus, the scores from the follow-up assessments may reflect the tests ability to detect a history of neglect in a patient rather than the concurrent occurrence and severity of neglect.

The above results indicate that in the post-acute phase after stroke, the use of a battery of conventional paper-and-pencil tests of VSN seem to provide a good to acceptable accuracy in detecting VSN (Halligan et al., 1989; Nijboer, Kollen, & Kwakkel, 2013; Lindell et al., 2007). In many cases it may also be more practical and appropriate to utilize the relatively simple paper-and-pencil tests in these early stages as it is often difficult for patients with more severe symptoms to perform complex computerized tests. On the other hand, at later stages following a stroke the conventional paper-and-pencil tests might be less sensitive to assess neglect (Jehkonen, 2002; Rengachary et al., 2009). Overall, reaction time paradigms seems to be more sensitive to the symptoms of VSN than paper-and-pencil tests, and especially so to subtle and/or residual symptoms which can pass undetected by conventional tests (Bonato & Deouell, 2013; Lundervold, Bergmann, & Wootton, 2005; Rengachary et al., 2009; Sacher et al., 2004; Schendel & Robertson, 2002). However, by including more complex tests in the early phases after stroke, the risk of missing data increases (e.g., Cumming, Brodtmann, Darby, & Bernhardt, 2012; Lesniak, Bak, Czepiel, Seniów, & Czlonkowska, 2008)

Some Models of VSN

Several different, but not necessarily mutually exclusive, models of visuospatial neglect have been proposed (Heilman et al., 1993; Kerkhoff, 2001; Marshall, Halligan, & Robertson, 1993). Early theories of VSN suggested that disorders of motor and/or sensory functions (e.g., visual field deficits), in combination with general intellectual impairments following a brain damage, was the mechanism underlying VSN. However, VSN is often observed without damage to the primary sensory/motor areas. Bisiach and colleagues (Bisiach, Capitani, Luzzatti, & Perani, 1981; Bisiach et al., 1979) proposed an account of VSN in which the primary disorder is to be found in the creation and storage of a spatially correct internal representation of contralesional space. The ability to store such a representation was suggested to be largely lateralized to the right hemisphere. Thus, there would be no contralesional space to be aware of. However, not all VSN patients show impairments in representational space (Heilman et al., 1993). Another theory suggests an action-intention deficit, a failure in initiating and sustaining limb movements toward contralesional space, even when blindfolded (Heilman et al.). On the other hand, patients with VSN also exhibit asymmetric performance in tasks that do not require manual responses (Bisicah et al., 1979).

Attentional Models

In a review of theories of visuospatial neglect Marshall and coworkers (1993) found that attentional models were the most common. This is probably due to the fact that many of the symptoms of VSN seem to be closely associated with attentional functioning and as such several different attentional theories of the mechanisms underlying VSN have been proposed (Kerkhoff, 2001; Mesulam, 2000; Parton et al., 2004; Posner, Walker, Friedrich, & Rafal, 1984).

Spatially Lateralized Attentional Deficits

Initial spontaneous ipsilesional orientation of attention (ipsilesional bias) can be seen in VSN patients as a tendency to start further to the right in conventional paper-and-pencil tests as compared to many right hemisphere patients without VSN and most healthy controls (Jalas et al., 2002; Kettunen et al., 2012; Mattingley, Bradshaw, Bradshaw, & Nettleton, 1994; Nurmi et al., 2010; Samuelsson et al., 1996). Such an ipsilesional bias has also been linked to the observations that many right hemisphere damaged stroke patients tend to orientate the position of their eyes and head towards the right (Fruhmann-Berger & Karnath, 2005; Karnath & Rorden, 2012). Karnath and colleagues observed this ipsilesional deviation even in patients at rest and in patients searching for non-existing targets in the dark (Fruhmann-Berger, Johannsen, & Karnath, 2008; Karnath & Fetter, 1995). Moreover, in studies that have measured eye movements on tasks containing multiple stimuli, it has been found that right hemisphere patients tend to start their search towards the right side (Behrmann, Watt, Black, & Barton, 1997; Gainotti, De Luca, Figliozzi, & Doricchi, 2009; Olk, Harvey, & Gilchrist, 2002).

As mentioned above, another symptom of a lateralized deficit is the asymmetry of target omissions often exhibited by VSN patients in conventional cancellation tasks. Other examples of asymmetric exploration in VSN patients have been shown in eye-tracking studies in which the visual searches of patients with VSN are mostly concentrated towards the right hemi-space (Fruhmann-Berger et al., 2008; Niemeier & Karnath, 2000). Asymmetry of visual explorations have also been demonstrated as slower reaction times (Bartolomeo, 1997; Olk et al., 2002; Rengachary et al., 2009; Schendel & Robertson, 2002) and eye saccades (Natale, Marzi, Bricole, Johannsen, & Karnath, 2007; Olk et al.) to targets presented in the left compared to the right hemi-space, and slower reorientation of attention towards targets localized more leftwards (Sacher et al., 2004).

Studies have also shown that an ipsilesional bias may occur separately from asymmetry in target omissions (Gainotti, D'Erme, & Bartolomeo, 1991; Jalas et al., 2002; Nurmi et al., 2010; Samuelsson et al., 1996) and that it may persist at follow-up even when patients no longer display asymmetry in omissions (Bartolomeo, 1997; Kettunen et al., 2012; Mattingley, Bradshaw, et al., 1994; Olk et al., 2002; Samuelsson et al.), indicating less severe or residual VSN.

A number of different attentional models have provided accounts for the asymmetric impairment seen in VSN (Halligan & Marshall, 1998; Heilman et al., 1993; Karnath, 1988; Mesulam, 2000; Robertson, 1993). The orientational bias model by Kinsbourne (1970, 1977) is often referred to as central in explaining the asymmetric performance seen in patients with VSN. Kinsbourne (1993) suggested that the two brain hemispheres orient attention to objects in the contralateral side of space. That is, the right hemisphere directs attention to objects in left visual space and vice versa for the left hemisphere. An important component in Kinsbourne's model is that the orienting systems of the two hemispheres balance each other through mutual reciprocal inhibition. A unilateral lesion to one of the hemispheres creates an imbalance which leads to an increased relative influence on orientation of attention by the opposite hemisphere. That is, an infarct in the right hemisphere results in an uninhibited activity in the left hemisphere's orienting system. This imbalance between the left and right orienting systems result in a spontaneous bias towards the right side. Kinsbourne proposed that this ipsilesional bias works as an attentional gradient resulting in a gradual decrease in the ability to detect objects from the ipsilesional side towards the contralesional side. Thus, according to Kinsbourne, attention is biased ipsilesionally across objects in the entire visual space rather than restricted to the contralesional half of space following a unilateral lesion. This account can explain the common finding of ipsilesional bias in patients with VSN (Gainotti, 2010; Jalas et al., 2002; Samuelsson et al., 1996).

A recent influential model was presented by Corbetta and co-workers (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; He et al., 2007). This model is mainly based on observations made in neuroimaging studies. Corbetta and co-workers suggested that VSN reflects damage to two separate, but interacting, visual attentional networks; a bilateral dorsal system for orienting attention to objects in contralateral space and a ventral system responsible for detection and reorientation of attention to unexpected and unattended stimuli across the entire visual space. Accordingly the ventral network might be viewed as having a "circuit breaking" function on the current attentional focus. This function of the ventral network is mainly lateralized to the right side of the brain. Using functional MRI Corbetta and colleagues have found that unilateral structural damage to the right ventral regions, aside from creating problems in detecting unattended stimuli, can temporarily impair the function of the right dorsal network. That is, as the right ventral areas are damaged, the intra-hemispheric signaling from the ventral to the dorsal network is disrupted. This disruption in the communication within the right hemisphere results in a functional imbalance between the right (relatively hypo-activated) and left (relatively hyper-activated) dorsal networks. The behavioral outcome of this imbalance is a spontaneous orientation of attention towards ipsilesional space in combination with deficits in the ability to detect stimuli. That is, attention is focused on targets at the outer ipsilesional side while stimuli outside focus, mainly towards contralesional side, are omitted.

Corbetta and Shulman (2011) and Karnath and Rorden (2012) have suggested that the lateralized deficit in neglect is related to a bias in the egocentric/viewer centered reference frame, caused by the right hemisphere damage. In short, according to Corbetta and Shulman, damages to the right hemisphere lead to a functional imbalance in the visual attentional network (as described above) with a rightward attentional bias as a consequence. This rightward bias may then shift the perceived egocentric midline towards the right. According to Karnath and Rorden, damage to the right perisylvanian network affects structures that are important for the egocentric reference frame and the damage may lead to a rightward shift of the patient's subjectively experienced egocentric body midline. As a result the patient's attention is also shifted towards the right.

Spatially Nonlateralized Attentional Deficits

Recent research into the VSN phenomenon has suggested that nonlateralized attentional deficits might influence the neglect symptoms in an essential manner (Husain & Rorden, 2003). Several of the above models, seeking to describe the ipsilesional bias and asymmetric explorations, seem to fall short when it comes to explaining the nonlateralized symptoms associated with VSN, and why VSN is more severe and lasting following right hemisphere damages compared to left hemisphere damages (Robertson, 1993). However, the model described by

Corbetta et al. (2005) postulates that damage to the ventral attentional system in the right hemisphere (described above) is connected with general (i.e. nonlateralized) symptoms of impaired reorientation of attention and omissions of targets outside the current focus of attention. Furthermore, damage to the brain-areas that are important for the ventral attentional network has also been associated with general impairments in arousal/alertness (see Corbetta & Shulman, 2011). The term arousal is related to the general intrinsic level of alertness or readiness to process external stimuli relative to optimal performance (Posner, 2008; Sturm & Willmes, 2001). Reduced arousal/alertness has been described as a possible component behind slowed perceptual processing of stimuli across the visual field and impaired sustained attention (Gerritsen, Berg, Deelman, Visser-Keizer, & Meyboom-de Jong, 2003; Howes & Boller, 1975; Robertson, 2001).

Robertson (1993, 2001) proposed that damage to an arousal mechanism, thought to be mainly lateralized to the right hemisphere, is necessary, but not sufficient, in explaining severe and lasting VSN. A close relationship between low general attentional capacity and VSN severity or persistence has been observed in several studies of nonlateralized components of attention, such as processing speed, sustained attention and effects of increased attentional load (Aglioti et al., 1997; Husain, Shapiro, Martin, & Kennard, 1997; Robertson & Frasca, 1992; Robertson, Manly, et al., 1997; Samuelsson et al., 1998; van Kessel et al., 2010). Other results also indicate that VSN, at least transiently, can be reduced through experimental modification of nonlateralized attentional symptoms (Robertson, 2001; Robertson, Mattingley, Rorden, & Driver, 1998; Robertson, Tegner, Tham, & Lo, 1995). The right brain might be dominant for some of these nonlateralized attentional components. Howes and Boller (1975) showed that simple unwarned reaction times were almost twice as long in patients with right- compared to left hemisphere damaged patients. Also, in a review of studies investigating hemispheric differences in nonlateralized attention functions, Robertson (1993) concluded that the right hemisphere seems to be specifically involved in maintaining attentional alertness. Impairments of these types of attentional capacity in RBD patients with VSN is thought to negatively influence the ability to compensate for the orientational bias of attention symptomatic for visuospatial neglect, thus playing a role in persisting neglect symptoms.

Interactions between lateralized and nonlateralized symptoms of VSN.

In accordance with the above descriptions of the clinical presentation of neglect, the severity of lateralized and nonlateralized attention symptoms has been found to be positively correlated both post-acutely (Buxbaum et al., 2004; Husain & Rorden, 2003; Husain et al., 1997;

Malhotra et al., 2005; Robertson, Manly, et al., 1997) and at later stages post-stroke (Bonato, Priftis, Marenzi, Umiltà, & Zorzi, 2010; Hjaltason, Tegner, Tham, Levander, & Ericson, 1996; Robertson & Frasca, 1992; Samuelsson et al., 1998; van Kessel et al., 2010).

Further evidence for the important interaction between lateralized and nonlateralized attentional symptoms comes from studies which show transient ameliorations of the spatial bias in VSN patients through manipulation and training of nonlateralized functions (DeGutis & Van Vleet, 2010; Robertson et al., 1998; Robertson et al., 1995; Sturm et al., 2004; Thimm, Fink, Kuest, Karbe, & Sturm, 2006) and by reports showing that signs of a lateralized bias can be found in healthy participants following experimental manipulations of nonlateralized attention functions (Fimm, Wilmes, & Spijkers, 2006; Manly, Dobler, Dodds, & George, 2005; Matthias et al., 2009).

Pattern of Recovery from VSN

The pattern of recovery in VSN has been described in previous studies. Based on conventional tests of VSN, about one third of patients with neglect in the first weeks after stroke have been found to show persisting VSN three months or more after stroke (Cassidy, Lewis, & Grey, 1998; Karnath, Rennig, Johannsen, & Rorden, 2011; Samuelsson et al., 1998). Also, the initial severity of neglect is positively related to the probability of persisting neglect at a later stage post-stroke (Black et al., 1995; Karnath et al.; Stone, Patel, Greenwood, & Halligan, 1992). In a neuroimaging study, Corbetta and colleagues (2005) described that in patients who recover from neglect, the imbalance between the dorsal networks in the right and left hemispheres (see earlier description of dorsal attentional networks) becomes rebalanced, whilst in patients with chronic VSN the imbalance is persistent. The authors concluded that persisting symptoms of VSN probably require impaired function in both the ventral and dorsal attentional network in the right hemisphere.

Incomplete recovery from VSN.

Within the first months after stroke both complete and incomplete recoveries have been reported for patients with post-acute VSN (Farné et al., 2004; Hier, Mondlock, & Caplan, 1983; Jehkonen, Laihosalo, Koivisto, Dastidar, & Ahonen, 2007; Kettunen et al., 2012; Ringman et al., 2004; Wade et al., 1988). Cassidy and colleagues (1998) assessed 66 acute right hemisphere stroke patients with conventional tests of VSN within 7 days post-onset and at monthly intervals for three months. By dividing each test sheet into 6 columns from left to right they could measure the relative recovery pattern of asymmetry in omissions. Overall, the authors found substantial improvements in terms of omissions during the three months. Recoveries were observed in both the left and right hemi-spaces, but omissions, especially in the left hemi-space, were still present, thus suggesting persisting lateralized inattention.

Nijboer, Kollen et al. (2013) studied the time course of recovery from neglect with a cancellation test in a selected sample of 101 stroke patients (including both right and left hemisphere damages). Initial assessment was done within 14 days after stroke, thereafter measurements were done at different intervals during the following year. Overall, the results showed that at 3 and 12 months after stroke, 46% and 40% of the initial neglect patients still had persisting symptoms of VSN in this test. Marked average improvements were observed in the neglect group for the number of contralesional omissions within the first three months. At three months a trend change was observed and the recovery rate leveled out. Following this trend change only smaller improvements were found. Despite the large improvements by the neglect patients as a group, their performance did not reach the performance of non-neglect patients during the first year after stroke. A similar pattern of recovery was seen for ipsilesional target omissions. However, for these omissions the initial difference between neglect and non-neglect patients was smaller. A trend change in recovery from ipsilesional omissions in the neglect group was indicated at 20 weeks post stroke. At this point the performance of the neglect patients closely approached the non-neglect patients' performance. Interestingly, after the trend change no further improvements were observed and the performance of the neglect group was close to, but did not quite reach, the level of the non-neglect group. In fact, visual inspection of the recovery line from 20 weeks to one year after stroke indicates a slight tendency of declining performance in the neglect group.

Variability in recovery from VSN.

Even though the symptoms observed in conventional tests tend to diminish within the first few months after stroke, large variations in the patterns of improvements have been observed (Appelros, Nydevik, Karlsson, Thorwalls, & Seiger, 2004; Cassidy et al., 1998; Farnè et al., 2004; Ferro, Mariano, & Madureira, 1999; Kettunen et al., 2012; Lundervold et al., 2005; Wade et al., 1988). For instance, Appelros and coworkers prospectively assessed consecutive patients (n = 36) who showed left-sided neglect. They were assessed at 2-4 weeks, at 6 months, and at 12 months after stroke with a battery of tests aimed at identifying personal and visuospatial neglect and neglect of far space. In 18 patients the authors observed deterioration in at least one symptom of neglect across the different assessments (patients with recurring stroke were excluded).

Jehkonen et al. (2007) identified fluctuations in recovery in a group of VSN patients (n = 4) across one year after stroke. From 10 days post-stroke to a three month follow-up these patients showed an improvement to no neglect on the sum score in the BIT tests. However, at a 6 month follow-up, all patients had scores indicating VSN. Further, at a 12 month follow-up, two patients still had scores below cut-off for neglect. At the acute stage this group of patients was found to have more severe neglect than a contrasting group of patients that, at some point after the initial assessment, showed stable recovery from neglect.

Recovery from Lateralized Symptoms of VSN

In the study by Rengachary et al. (2009), patients with VSN at two weeks after stroke showed slower reaction times for targets than controls, both at baseline (two weeks after stroke) and at follow-up (about 9 months after stroke) in both visual fields. This reaction time impairment was worse in the contralesional (left) field indicating an asymmetric bias in the attentional deficit. The patients showed significant improvements in both visual fields at the follow-up, but the reaction times did not improve to the level of controls, and the patients still had slower reaction times to targets in the left compared to the right field. Similar results were reported by Farné and colleagues (2004). These authors assessed 33 right hemisphere damaged patients, with a mean age of 68 years, at 1-6 weeks after stroke and again at one and two weeks thereafter with a battery of conventional paper-and-pencil tests and computerized tasks of spatial and nonspatial attention. A sub-group of 8 patients, who were identified as having neglect initially, was also assessed at a later stage (>3 months post stroke). In the conventional tests the authors found statistically significant or near significant improvements in the neglect patients lateralized symptoms. However, the magnitude of recovery did not bring the neglect patients to the same level of performance as shown by the non-neglect patients. At the later stage follow-up, the left-sided performances were found to be comparable to the initial score (at 1-6 weeks) of the non-neglect patients in two out of the three conventional VSN tests. The results of Farné et al. (2004) and Rengachary and colleagues (2009) are somewhat difficult to interpret as they did not differentiate patients who recovered from neglect from those with persistent neglect.

Rengachary, He, Shulman, and Corbetta (2011) investigated possible differences of performances between VSN patients who showed recovery from neglect and patients who exhibited neglect both at two weeks and at about 9 months after stroke. VSN symptoms were classified as present if the patient presented with scores below cut-off in at least two of 6 paper-and-pencil tests. Both groups showed an asymmetry in their reaction times (increased reaction times to the left), but for the patients who did not show recovery from neglect, the reaction time asymmetry at the acute assessment was significantly higher. The same pattern was observed at follow-up, albeit less marked. At follow-up, both groups showed significant improvements with regard to reaction time differences between the left and right visual field. However, compared to the controls, impairments were still present in both patient groups at the follow-up. This is in support of the argument that initial severity of neglect is related to later persistent neglect (Black et al., 1995; Karnath et al., 2011; Stone et al., 1992).

Recovery from Nonlateralized Symptoms Related to VSN

Farné et al. (2004) found that neglect and non-neglect patients, compared to healthy controls, showed impaired nonlateralized performances, as measured by reaction times in sustained attention and alertness tasks. Further, only non-significant improvements were observed in the first weeks after stroke in both patient groups, indicating less recovery in the non-lateralized relative to the lateralized symptoms (see above for a description of recovery from lateralized symptoms).

Rengachary et al. (2009) found that the VSN patients had marked recovery in overall reaction time to targets in the Posner Cueing paradigm. However, even at the 9 month follow-up, the performances of the patient group showed large variability, possibly reflecting differences in recovery within this group.

Samuelsson and colleagues (1998) separated "recovered" from "not recovered" neglect patients (assessed at 1-4 weeks and 6-7 months after stroke). In a simple warned auditory reaction time task the recovered patients showed significant improvements in performance, approaching a level close to that of controls and patients without a history of neglect. On the other hand, patients with persistent neglect showed no improvement in this task.

Taken together the literature reviewed in this thesis suggests that residual symptoms of spatially lateralized and nonlateralized symptoms may exist even in patients who do not show VSN at later stages after stroke. The sensitivity in detection of such subclinical symptoms seems to be dependent upon the characteristics of the tests used to assess VSN (Rengachary et al., 2009).

Functional Outcome

The International Classification of Functioning, Disability and Health model (ICF; World Health Organization, 2001) presents a framework for describing health that is based on reciprocal relationships between differentiated domains of body function and structure, activities, personal and environmental factors, and participation. Similarly, the rehabilitation and functional outcomes of stroke patients have been associated with a multitude of factors which can be related to the ICF domains, such as pre-stroke status and physical (Brewer, Horgan, Hickey, & Williams, 2013), social (Daniel, Wolfe, Busch, & McKevitt, 2009), mental (Christensen et al., 2008) and cognitive (Wagle et al., 2011) barriers associated with sustaining a brain injury, and combinations of these factors. Accordingly, outcome in the different ICF domains can be measured in varying details and complexity. For instance, the different symptoms associated with VSN can be seen as related to the body function and structure domain of the ICF. Within the activity domain outcome can be related to, amongst others, basic - and instrumental activities of daily living (ADL; Roley et al., 2008). Basic activities of daily living are activities related to the degree of independence in performing personal care routines like going to the toilet, dressing, feeding, and different types of mobility and transfers within the home (e.g., from the bed to a wheelchair). Instrumental activities of daily living are related to an individual's ability to perform complex activities associated to interactions with the community and environment.

Functional Outcome in Relation to Cognitive Impairments

Cognitive deficits are common after stroke and different aspects of cognitive impairments have been identified as predictors of negative functional outcome (Hochstenbach, Mulder, van Limbeek, Donders, & Schoonderwaldt, 1998; Hurford, Charidimou, Fox, Cipolotti, & Werring, 2013; Nys et al., 2005). For example, Lesniak and colleagues (2008), using a cognitive screening battery, reported that at the post-acute stage (7-14 days after onset) 78% of the stroke patients had signs of impaired performance in at least one cognitive domain. Deficits related to the attentional domain were most frequently observed, both post-acutely and at the 1-year follow-up. In this study, initial functional impairment, age, and post-acute executive impairments were found to be significant predictors of poor functional outcome at one year after stroke.

Narasimhalu and colleagues (2011) assessed a large cohort of stroke patients at three months and up to 5 years post stroke. At the three month baseline, the patients were assessed with a neuropsychological test battery. From this battery the patients were classified as having mild deficits (no dementia) if 1 to 2 domains of test showed impairment, and moderate deficits (no dementia) if impairments were found in 3-6 domains. Outcome measures were assessed annually (for an average of 3.2 years) with full neuropsychological assessments and with regard to dependency with the modified Rankin Scale (dichotomized with scores > 2 indicating dependency). The authors found that baseline mild or moderate cognitive deficits, compared to no cognitive impairments, predicted dependency at follow-up. Further, when the different domains of cognition were analyzed in a multivariate regression, visuo-motor speed was found to be the only significant predictor of dependency. This study did not, however, control for any neurological factors. Stroke subtype (TOAST) was available, but was not included in the regression analysis.

Of the many cognitive deficits observed after stroke, attentional impairment might be an especially important predictor of outcome (Barker-Collo & Feigin, 2006) as attentional deficits of various types have been found to be related to negative functional outcome (Barker-Collo, Feigin, Lawes, Parag, & Senior, 2010; Lesniak et al., 2008; Lundquist, Alinder, & Rönnberg, 2008; McDowd, Filion, Pohl, Richards, & Stiers, 2003; Nys et al., 2005; Wagle et al., 2011; Wilson, Manly, Coyle, & Robertson, 2000).

Functional Outcome in Relation to VSN

Several studies have suggested that acute neglect, together with other symptoms, is associated with poor recovery and that it is an important predictor of functional outcome after stroke, especially in patients with RBD (Appelros, Karlsson, Seiger & Nydevik, 2003; Jehkonen, 2002; Jehkonen, Laihosalo, & Kettunen, 2006; Kotila et al., 1986; Paolucci et al., 2001, 1998).

Buxbaum and colleagues (2004) found that VSN, as assessed with 5 different conventional tests of neglect in 166 right hemisphere damaged rehabilitation in- and outpatients at 5-41 days post stroke, was a better predictor of poor functional outcome at discharge than overall stroke severity, as measured by the number of areas of the brain affected by the lesion. The study by Gillen, Tennen, and McKee (2005), showed that rehabilitation inpatients (assessed at admission about 2 weeks post stroke) with neglect had longer stays at the rehabilitation unit and progressed more slowly than patients without symptoms of neglect, even after controlling for functional status at admission. Similar results have also been observed for neglect patients that have received specific rehabilitation training for their VSN. Paolucci and coworkers (2001) concluded that patients who showed neglect at admission (about 5-6 weeks after stroke) were less likely to benefit from the rehabilitative treatment and to have more severe disability at discharge. If the neglect patients also show evidence of anosognosia, the outcome after rehabilitation seems to be even worse than for neglect alone (Gialanella, Monguzzi, Santoro, & Rocchi, 2013).

The role of VSN in long-term outcome.

Nys and co-workers (2005) assessed 111 stroke patients with regards to background variables, basic and instrumental activities of daily living, and a neuropsychological battery within 3 weeks and at 6-10 months after stroke. The neuropsychological assessment covered the domains of reasoning, verbal memory, executive functioning, visual perception and construction, visual memory, language and neglect. The authors found that 31% of the patients had long-term cognitive deficits, 19% had persisting low scores in basic ADL and 24% had low scores in instrumental ADL. Further, the results showed that neglect and visual memory were found to be independent predictors of dependency at follow-up.

Jehkonen and colleagues (2007) identified a group of patients (*n* = 4) with neglect at 10 days post stroke who showed incomplete improvement from VSN with scores fluctuating around cut-off (3 to 12 months after stroke). Another group of patients (*n* = 12) with neglect scores at or around cut-off for VSN at baseline, but with continuous improvement across the follow-ups, was also identified. The functional outcomes were compared between these two groups. Recoveries with regard to basic ADL and on neurological factors were similar in these two groups. On the other hand, the patients with fluctuating performance showed less recovery of participation in social activities. This difference was most marked within the first 6 months after stroke. According to the authors a possible reason for these results might be that the patients with fluctuating improvement from neglect may be able to use compensatory strategies during more structured neuropsychological assessments of neglect and in basic ADL whilst performances will suffer in demanding and complex activities of daily living.

Nijboer, van de Port, Schepers, Post, and Visser-Meily (2013) investigated if neglect (as measured by an asymmetry ratio of omissions in a cancellation task) at admission to a rehabilitation clinic (three to four weeks post stroke) could predict various domains of activities of daily living 6, 12, and 36 months after stroke. In this study corrections were made for motor and sensory impairments, dependence, and depression at admission. The results showed that at admission the neglect patients scored lower on relatively complex measures of functional independence (self-care, transfers and locomotion) compared to non-neglect patients. The marked differences between the two patient groups in the measures of functional independence were found to decrease as time passed after the stroke. Also, severity of neglect was found to be related to more severe problems in self-care and transfers.

Recently, Jehkonen and coworkers (2006) reviewed studies published between 1996 and 2005 on the impact of neglect on functional outcome. The authors found that 25 out of the

26 reviewed studies showed a negative influence of neglect on functional outcome. However, most of these studies failed to differentiate between different sub-types neglect. In those few studies that did differentiate between sub-types, none specified the possible influences of each sub-type on outcome separately.

Taken together, the studies referred to above suggest that neglect has strong associations with measures of functional outcome, especially when both neglect and outcome are measured relatively early following a stroke, and that neglect can provide predictive information regarding long-term outcome in stroke patients.

Functional Outcome and Lateralized and Nonlateralized Attentional Deficits

The attentional models of VSN described above (e.g., Corbetta & Shulman, 2011; Karnath & Rorden, 2012; Robertson, 1993, 2001) suggest that the VSN phenomenon can be divided into different key symptoms. The most basic division is into symptoms of lateralized and nonlateralized visual inattention. Accordingly, in conventional tests of neglect, combinations of the different lateralized and nonlateralized symptoms may be observed in patients with neglect. However, the different lateralized and nonlateralized key symptoms of VSN and their relationship to functional outcome have seldom been examined together in the same stroke sample (Kotila et al., 1986; Linden, Samuelsson, Skoog, & Blomstrand, 2005; van Kessel et al., 2010). The study by Kotila and co-workers is the only study, to our knowledge, that has aimed at comparing the relative importance of lateralized and nonlateralized inattention in relation to functional outcome. The authors found that only 1 of 7 patients with lateralized inattention became able to live independently during a four year follow-up, whilst 6 out of 7 patients with nonlateralized inattention lived independently already at three months post-stroke. These results suggest that nonlateralized and lateralized inattention at the early stage of stroke might predict different functional outcomes, but further studies are required to confirm this observation.

The classification of VSN sub-symptoms can be made more specific than just a dichotomization into lateralized and nonlateralized inattention. As described above, at least three core symptoms of VSN and several related symptoms have been identified. The attentional models outlined earlier in this review suggested multiple core components as essential in the VSN phenomenon, and several specific symptoms related to these components have been identified (Husain & Rorden, 2003). In the clinical setting the lateralized symptoms may be assessed through the ipsilesional bias at the initiation of the task and through a left-to-right asymmetry of target omissions. The nonlateralized symptoms may be assessed by the total number of omitted targets and by the speed in the accomplishment of the task. Nonlateralized symptoms may also be assessed as general deviations in the pattern of exploration of a visual array, such as repetitive identification of the same target during visual search.

The relationship between neglect and a negative functional outcome is frequently described, but knowledge about how the different sub-symptoms associated with visuospatial neglect are related to functional outcome is sparse. Mattingley, Bradshaw, and colleagues (1994) tested left hemisphere patients who had acute VSN on a battery of clinical and experimental tasks 12 months after stroke. This study found that most of the patients had recovered from the acute asymmetry in target omissions, but that the patients still exhibited an initial ipsilesional capture of orientation in attention. The authors suggested a relationship between the ipsilesional bias in the attentive behavior and an inferior functional recovery. Similarly, Webster and co-workers (1995) found that right hemisphere patients, from an inpatient rehabilitation unit, who showed ipsilesional bias but not asymmetry in target omissions, made more errors in a wheelchair maneuvering task than right hemisphere patients without any symptoms related to VSN. Thus, the authors concluded that ipsilesional bias alone might have clinical importance.

Research Objectives

Overall, the literature reviewed in this paper has found that the VSN phenomenon is associated with functional outcome after stroke. Some results also suggest that sub-symptoms related to an initial ipsilesional bias in the orientation of attention may have prognostic value. Furthermore, several studies reported a connection between nonlateralized attentional impairments and the severity and persistency of neglect. Accordingly, valuable prognostic and clinical information regarding functional outcome at later stages after stroke and recovery from VSN might be obtained by assessing the core asymmetric neglect symptoms and non-lateralized attentional symptoms related to neglect. However, few studies have been carried out focusing on the relative importance of these lateralized and nonlateralized symptoms regarding their relevance as predictors of long-term outcome. Moreover, in studies aimed at assessing different cognitive functions early after stroke with more complex tests, the patient samples tend to be selected and/or a relatively large proportion of the patients are excluded as they are not capable of accomplish the test session (Cumming et al., 2012; Lesniak et al., 2008).

The main objective of the current thesis is two-folded: 1) to investigate the prognostic value of the use of basic clinical tests at the early post-acute stage in order to predict short time and longer time functional outcome and 2) to investigate if the division of the clinical neglect phenomenon into a number of fundamental lateralized and nonlateralized symptoms will enhance the value of these tests in the prediction of outcome. A second objective is to describe the pattern of change of these lateralized and nonlateralized symptoms across the initial months after the stroke event.

Aims of the Studies

Study I.

Study I investigated lateralized and nonlateralized inattention in a large prospective and consecutive sample. The aims of the study were to describe 1) the occurrence and course of lateralized and nonlateralized inattention, 2) the pattern of neurological symptoms and neuroradiological findings in the groups with lateralized and nonlateralized inattention, and 3) the functional outcome in these two groups and the influence on the outcome by neurological symptoms.

Studies II-IV.

These studies investigated lateralized and non-lateralized symptoms related to VSN and processing speed in conventional clinical tests of neglect and visual search.

Study II.

The aim was to analyze the relative importance of core components and related symptoms of VSN as predictors of functional dependency three months and two years following right hemisphere stroke. Included were three basic sub-symptoms of VSN (initial ipsilesional bias in orientation, omissions, and asymmetry of omissions) and two symptoms related to VSN (processing speed and repetitions of previously detected targets in visual searches). The analyses were made after controlling for overall severity of neurological deficits.

Study III.

The aims were: 1) to describe the patterns of recovery in the individual lateralized and nonlateralized symptoms of VSN from post-acute to three months after stroke, 2) to explore the relative importance of the post-acute scores of VSN and processing speed in relation to the overall neglect severity at three months, and 3) to explore the relative strengths of the concurrent associations between the individual lateralized and nonlateralized VSN symptoms and functional dependency at three months. The analyses were made after controlling for the effect of overall neurological symptoms.

Study IV.

This report examined the relative importance of symptoms related to VSN as predictors of long term functional outcome seven years after a right hemisphere stroke. The potential predictors were assessed at the post-acute stage and include both nonlateralized (omissions and processing speed) and lateralized (initial ipsilesional bias and asymmetry in omissions) symptoms. Furthermore, overall neurological impairment post-stroke as well as general cognitive level and years of education at the 7 year follow-up were investigated. The aims were to investigate these symptoms' relative importance as predictors of: 1) functional dependency at seven years post-stroke and 2) overall level of activity in domestic, leisure/work and outdoor activities seven years post-stroke.

METHOD

Participants

The participants were recruited from the Sahlgrenska Academy Study on Ischemic Stroke (SAHLSIS). Details of SAHLSIS have been described elsewhere (Jood, Ladenvall, Rosengren, Blomstrand, & Jern, 2005). Briefly, patients who presented with first-ever or recurrent acute ischemic stroke before reaching the age of 70 years were recruited consecutively at four Stroke Units in western Sweden. The inclusion criteria were: (a) acute onset of clinical symptoms of suggestive stroke, and (b) no hemorrhage on computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain.

The current studies were based on patients included in the SAHLSIS from the Stroke Unit at the Neurological Department at the Sahlgrenska University hospital between August 1998 and December 2003. A neurologist (KJ), blind to the scores in the other variables, reviewed the patients MRI/CT reports and the neurological clinical symptoms in the medical records to establish the hemispheric localizations of the damage and the presence of previous lesions. The studies were approved by the Ethics Committee at the University of Gothenburg. All participants provided written informed consent prior to enrolment. For participants who were unable to communicate, consent was obtained from their next-of-kin. Patients were included regardless of previous cardiovascular or cerebrovascular events.

In Study I a consecutive series of 375 patients were included. The patients were included regardless of the location of the brain lesion. Of the 375 participants 53 were not tested on the neglect test, 29 due to severe impairments, 12 due to subtle symptoms, and two were admitted to another department or hospital. The reason for missing data could not be established in 10 participants and there were insufficient data to allow for retrospective classification of visual inattention in 11 participants. Thus, 364 patients were investigated in Study I.

At the start of Study I only one test of neglect was included and the patients were not investigated for processing speed, ipsilesional bias in attention and other central aspects that were used in Studies II - IV. Thus, for these three studies the included patients were selected from a consecutive series of patients starting at the first patient with data on these additional measures. This selection resulted in 297 patients. From this series of patients, only those with neuroradiological (MRI/CT) and/or clinical signs of an acute right hemisphere stroke were included in Study II-IV. Patients with signs of acute right hemisphere stroke and additional signs of cerebellum, brainstem and/or previous brain damages were also selected. Eligible patients with a right hemisphere index stroke were 105. Figure 1 describes how these 105 patients were included in Studies II-IV. The figure describes the longitudinal characteristic of SAHLSIS. The SAHLSIS is a prospective study in which the patients are investigated several times (post-acutely, and about 3 months, 2 years, and 7 years) after the index stroke. The patients are followed regarding survival and recurrent vascular events and information is collected as to the reasons for missing data. Due to new stroke, deaths, and missing data the number of included patients were 95 to 86 at the three months assessments (Studies II and III), 87 at the 2 year follow-up (Study II), and 57 at the 7 year follow-up (Study IV; see Figure 1).

The present Studies (I-IV) include data from the post-acute stage and the three different follow-up assessments, and the patients were assessed with the following variables:

- *Baseline (post-acute)*: lesion location, vascular supply area and aetiology of the stroke, neurological deficits and symptoms of visuospatial neglect and symptoms related to neglect.
- *Three months:* neurological deficits, the modified Rankin Scale, symptoms of VSN and symptoms related to VSN.
- *Two years*: the modified Rankin Scale.
- *7 years:* the modified Rankin Scale, the Frenchay Activities Index and the Mini-mental State Examination.

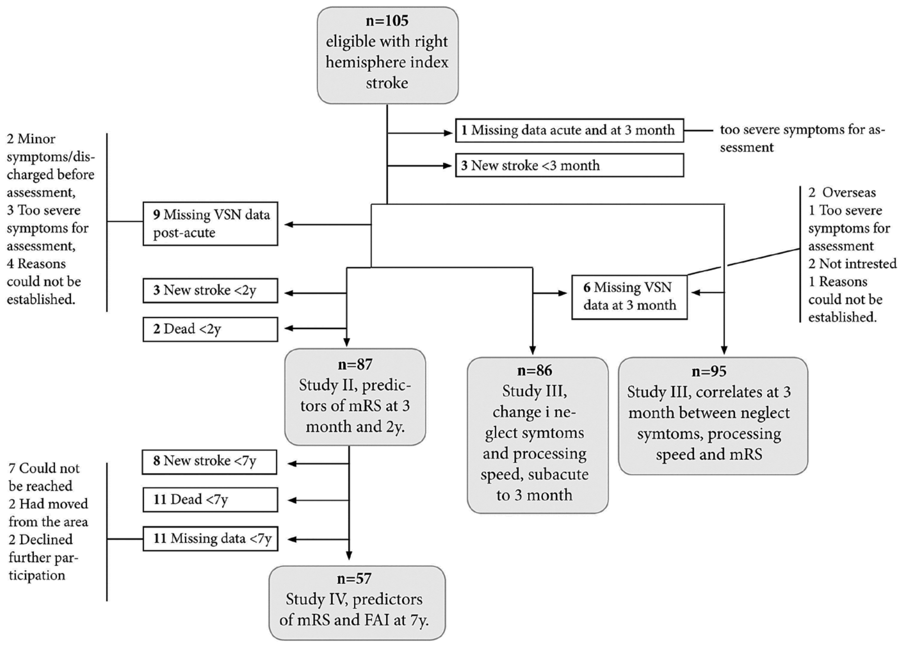

Figure 1. Schematic overview of eligible participants and patients with missing assessments or who were excluded for Studies II – IV.

Table 1 show the background data for the patients in Study I and Studies II-IV separately.

Table 1

Background Data

	Study I	Studies II - IV
No.	375	105
Age at admission (*M*/*SD*/Range)	54.5 / 10.9 / 18-69	54.2 / 11 / 18-69
Gender (m/f)	237 / 138 - 63.2% / 36.8%	57 / 48 - 54.3% / 45.7%
No. retrospectively classified	42 - 11.2%	-
Days onset > assessment	8 / 5.5 / 1-51	7.3 / 5.3 / 1-45

Abbreviations: No. = number of patients, *M* = mean, *SD* = standard deviation, m = male, f = female.

Tests and Measures

Star Cancellation Test (SCT; Studies I - IV)

The SCT is a paper and pencil subtest of the Behavioural Inattention Test (BIT) by Wilson, Cockburn, & Halligan (1987). This battery is standardized and has good reliability (Halligan, Cokburn, & Wilson, 1991). The BIT was designed to measure visual neglect symptoms related to attentional deficits in patients with brain damage. The SCT consists of 56 small stars in an array of distracters (large stars, letters and short words) on a landscape A4 sheet. The short words were translated from English into Swedish. Two of the small stars in the mid-line of the test were used to demonstrate the cancellation procedure. The participants were instructed to cross out all small stars on the sheet (27 at each side of the mid-line). The SCT can be divided into 6 vertical columns with 11 targets in the two central columns and 8 targets in each of the two outer right- and left-hand side columns.

Letter Cancellation Test (LC) (Studies II - IV)

The LC test is another paper and pencil subtest of the BIT with 40 targets consisting of the letters “E” and “R” spread among distracter letters in five lines on a landscape A4 sheet. A modified version of the test was used in which the participants were instructed to perform the test as fast and accurate as possible and the time used to finish the task was recorded by the examiner. The LC test can be divided into 4 vertical columns, each containing 10 targets.

Star Cancellation Test-B (SCT-B; Studies II –IV)

The SCT-B is not included in the BIT, but is a mirrored copy of the SCT described above. The SCT-B was administered with a time limit of 30 seconds. As in the SCT the SCT-B can be divided into 6 vertical columns. Participants were asked to cross out as many targets as they could find within the time limit.

Visual Search for Letters and Numbers (VS-L/N; Samuelsson, Hjelmquist, Jensen, & Blomstrand, 2002; Studies II - IV)

The test consists of 32 targets (16 single letters and 16 single digits). The targets are spread pseudo-randomly throughout a landscape A4 sheet. Participants were asked to read out loud all the letters and numbers on the sheet. The VS-L/N can be divided into 8 vertical columns, each containing 4 targets.

Visual Search for Short Words (VS-W; Johannesson, 2002; Studies II - IV)

In this test 36 two-letter words are spread pseudo-randomly on a square (30cm X 30cm) test sheet. Participants were asked to read all the words on the sheet. The VS-W can be divided into 6 vertical columns, each containing 6 targets.

Based on the performance in the tests described above symptoms of visuospatial neglect were identified and measured as follows:

Study I

Omissions.

Based on the performance of 25 controls without brain damage (*Mdn:*57 years; range: 29-70 years) from an earlier study (Samuelsson et al., 1995), scores of 52 or less on the SCT were interpreted as indicating the presence of visual inattention (VI; see also Lindell et al., 2007). Patients who scored above cut-off were classified as having no visual inattention (NoVI). The SCT was chosen for Study I as it has been shown to be among the most sensitive clinical tests of VSN (Halligan et al., 1989; Lindell et al.), and as the SCT is a non-verbal cancellation test, it was selected to increase participation of patients with aphasia.

Asymmetry of omissions.

Patients omitting at least three more targets within one horizontal half of the test sheet compared to the opposite half of the SCT were classified as showing lateralized visual inattention (LVI).

Study II

Repetitions of detections.

The number of repeated detections of previously identified targets was recorded in the VS-W and VS-L/N tests. The average percentages of repetitions from these tests were calculated for each participant.

Studies II - IV

The assessment of neglect symptoms in Studies II-IV was based on a battery of tests. This made it possible to include continuous data as measures of omissions, asymmetry of omissions, ipsilesional bias and repetitions of detections.

Omissions.

The average percentage of omissions ([total omissions x 100] / 162 targets) across the tests SCT, LC, VS-W and VS-L/N was calculated for each participant. The SCT-B was not included in the measures of omissions and asymmetry of omissions (see below). This exclusion was done due to the time limitation in this task. The omissions in the SCT-B might reflect slow processing speed rather than inattention of stimuli.

Asymmetry of omissions.

The "Center of Cancellation" index (CoC; Rorden & Karnath, 2010) provides a measure of asymmetry of the detected targets based on a baseline corrected average center of mass calculation. As such, it produces a severity measure of asymmetry which is sensitive to both the total number and the location of omissions. The CoC indexes asymmetry of omissions on a scale from -1 to +1. If a participant only identifies targets on the outer right-hand side of a test the CoC score will be close to +1, conversely, if a patient only identifies targets on the outer left-hand side of a test the CoC score will be close to -1. Further, a CoC score that is close to

.5 would mean that the patient omitted most of the targets in the left half of the test sheet and identified most of the targets in the right half of the test sheet. Similarly, a CoC close to .75 describes a patient who omitted targets in the left-most ¾ of the test sheet. CoC scores close to 0 indicate that the participants either omitted few targets, omitted targets in similar positions but on opposite sides of the test, or targets close to the vertical center-line of the test sheet. The Center of Cancellation was chosen as it is suggested to be a more reliable indicator of asymmetry severity compared to other methods such as counting omissions in one half only or the entire test sheet or, dividing detected targets in the contralesional half of the test sheet with the total number of detected targets (Rorden & Karnath; Suchan et al., 2012). The average CoC was calculated across the tests SCT, LC, VS-W and VS-L/N.

Initial ipsilesional bias.

The start column of searches/cancellations in each of the tests SCT, LC, SCT-B, VS-W and VS-L/N was recorded. As the number of columns differed between the tests, ipsilesional bias was coded as "1" if the search/cancellation started in the far left-hand column, as "2" if it started in the left half of the test, but not in the far left-hand column, as "3" if it started in the right half of the test, but not in the far right-hand column, and as "4" if it started in the far right-hand column of the test. The average ipsilesional bias was calculated for each participant.

Visual processing speed.

Two separate measures of processing speed were calculated. One was the number of omissions in the time-limited SCT-B and the other measure was seconds per identified target in the LC test.

Study III

Cut-off scores for impaired performance.

The estimations of impaired performance in the four variables above were done in two steps. First, a cut-off for each variable (omissions, asymmetry, ipsilesional bias, and processing speed) was established for each of the relevant individual tests. Second, an average cut-off for each variable was calculated based on the individual cut-offs in each test. Table 2 depicts the estimated individual and average cut-off levels for the variables of VSN and processing speed.

Cut-off scores for omissions.

For omissions, the cut-off score in each test was defined as one target omission more than the lowest score observed in a healthy control group (Lindell et al., 2007; Samuelsson et al., 1995; see Table 2). For the Star Cancellation Test and Letter Cancellation test the cut-offs adopted in the current study came from a control group of 31 adults (mean age = 55 years, *SD* = 13.4) without any history of neurological deficits, alcoholism, or psychiatric illness (Lindell et al.). For the two tests of visual search the cut-offs were obtained from the results of an unpublished control group (see below).

Average cut-off for omissions across all tests.

The lowest observed scores in controls in each test were summed and one omission was added to represent ≥ cut-off value in terms of omissions (7+1 = 8; see Table 2). Thus, the ≥ cut-off score in percentages was 5% ([8 * 100] / 162).

Cut-off scores for asymmetry.

There are no published normative data regarding what constitute impaired performance in the CoC for the tests used in this study. However, Rorden and Karnath (2010; Karnath et al., 2011) suggested that CoC scores >.09 as indicative of neglect in two other paper-and-pencil cancellation tasks.

To estimate cut-off scores in the CoC for the tests applied in the current study, re-calculations based on published cut-off scores of a different measure of asymmetry were done. First, each patient's COC scores and their laterality of omissions score (the number of identified targets in the left half of the test sheet, divided by the total number of detected targets [Friedman, 1992; Lindell et al., 2007]) were calculated for each of the four tests. In the laterality of omissions score, a score below .5 indicate neglect for left sided targets and a laterality score above .5 indicate neglect for right sided targets. In healthy controls the range of this laterality score has been reported to be in the range of .49 - .51 for the Star Cancellation Test and .47 - .56 for the Letter Cancellation Test with a .01 score outside these ranges indicating impaired performance (Lindell et al.).

Second, to estimate the laterality cut-off scores in the two visual search tasks, two separate linear regressions were performed. In the first regression the laterality scores from the SCT and LC were predictors whilst the laterality score of the VS-W was the criterion variable. In the second regression the laterality scores from the SCT and LC test were predictors whilst the laterality score of the VS-L/N was the criterion variable. The estimated laterality scores indicating impaired performance, calculated from the regressions, were for the VS-W ≤ .47 and ≥ .54 and, for the VS-L/N ≤ .48 and ≥ .56.

Third, separate linear regressions for each test, with the laterality scores as predictors and the CoC score from the same test as criterion, were performed. The estimated cut-off scores for CoC in each test were calculated from the regressions (see Table 2).

Average cut-off for asymmetry across all tests.

The CoC cut-off scores from the tests were summed and a .001 point score was added to represent the ≥ cut-off value in terms of CoC score (.149 + .001= .150). Thus, the average ≥ cut-off score for CoC was .038 (.150 / 4).

Cut-off scores for ipsilesional bias.

The column (1 to 4) in which the patients marked the first cancellation or read out the first target was recorded by the test administrator. Cut-off values for ipsilesional bias in the two Star Cancellation Tests and the Letter Cancellation test were based on published results by Nurmi and co-workers (2010). In this study the authors used receiver operating characteristic analyses to estimate cut-off guidelines for what constituted normal performance in three cancellation tests, including the SCT and LC tests. The reported estimated normal performance for the SCT was more than 11.05 cm to the left of the midline of the test sheet and more than 10.05 cm to the left of the midline for the LC. With regards to the column differentiation in the current study (see above) the distances reported by Nurmi et al. corresponds to a start of cancellations within the leftmost column. Impaired performance in the two visual search tasks was indicated if a patient began reading at least one column to the right of the rightmost start column observed in a control group (unpublished results, see below).

Average cut-off for ipsilesional bias across all tests.

The lowest observed start column scores in the controls in each of the two visual search tests and the start columns of the cancellation tests related to normal performance were summed. A one point score was added to represent the ≥ cut-off value in terms of start column (7 + 1 = 8). Thus, the average ≥ cut-off score for start column was 1.6 (8 / 5).

Table 2

Cut-off Levels for Impaired Performance

	Core VSN symptoms		
Tests	Omissions	Asymmetry	Ipsilesional bias
Star Cancellation Test	> 1	>.029	> 1
Letter Cancellation	> 4	> .058	> 1
Star Cancellation Test - B	-	-	> 1
Visual search for short words	> 1	> .031	> 2
Visual search for letters/numbers	> 1	> .031	> 2
Average across all tests	≥ 8 (5%)	≥ .038	≥ 1.6

VSN = visuospatial neglect. The scores under omissions and ipsilesional bias are the lowest scores observed in the control groups. Scores under the heading "Asymmetry" are the calculated CoC cut-offs for asymmetry.

Impaired Performance in Processing Speed

Time per identified letter in the Letter Cancellation test.

The time per identified letter in the LC test interpreted as indicating an impaired performance in processing speed was set at a result slower than the slowest performing participant from a control group (unpublished control group, see below). The slowest performance observed in the control group was 2 seconds per identified target. Thus, impaired performance in this processing speed measure was indicated if a patient used > 2 seconds per identified target.

Number of omissions in the Star Cancellation Test-B.

The number of omissions interpreted as indicating impaired performance in the SCT-B was set at a score of one omission more than the worst performing participant in a control group (unpublished control group, see below). The highest number of omissions observed in the control group was 14. Thus, cut-off for this processing speed measure was 15 (≥ 28%) omissions.

Control Group

The results of the controls referred to above have not been published. The control group for the current study was an excerpt of 25 (12 females and 13 males) healthy adults with ages ranging from 29 to 70 years (mean age = 57, *SD* = 11.68) from a larger control group (*n* = 34) (Samuelsson, 1997; Samuelsson et al., 1995). The nine patients from this larger control group who were not included as controls in this study, were those with an age of 70 years or older. The results of the selected controls were used as reference scores for estimating impaired performance of omissions in the VS-W test and VS-L/N test, for ipsilesional bias in the test in which no cut-offs were published, and for processing speed in the LC test and SCT-B.

Pattern of Recovery in VSN and Inattention at Three Months Post-stroke (Study III)

In the analyses of change in performance across time the following two types of severity of symptoms were used: 1) the overall severity in terms of total number of test with scores worse than cut-off and 2) four general levels of severity (moderate to severe, mild, sub-clinical, and no symptom). Furthermore, the symptoms were classified as VSN or inattention. These procedures are described below.

The Classification of VSN and Inattention

Patients who had scores worse than cut-off in the measures of asymmetry and/or ipsilesional bias were sub-classified as showing symptoms of VSN whilst patients who had scores worse than cut-off in the measure of omissions only were sub-classified as showing symptoms of visual inattention.

The Severity of VSN and Inattention

The classification of severity of VSN and inattention post-acutely and at three months after stroke were based upon the number of tests with scores worse than cut-off. For the three core symptoms of VSN (omissions, asymmetry and ipsilesional bias) there was a total of 13 cut-off scores (4 for omissions, 4 for asymmetry and 5 for ipsilesional bias, see Table 2). Based on these cut-off scores a subdivision was made into four general levels of severity of symptoms (moderate to severe, mild, sub-clinical, and no symptoms). The symptoms were classified as

1) *moderate to severe* if they had a total of three or more scores worse than cut-off in at least one of the core symptoms, 2) *mild* if they had two scores worse than cut-off in at least one of the core symptoms, 3) *sub-clinical* if they had one score worse than cut-off in at least one of the core symptoms, except for in ipsilesional bias (see below for details), and 4) *No symptoms* if they had no score worse than cut-off in any of the variables, or one score worse than cut-off in ipsilesional bias. The reason for the different criteria regarding ipsilesional bias compared to omissions and asymmetry is that ipsilesional bias has been reported to occur even in some healthy controls (Nurmi et al., 2010).

Based on these levels of severity and classifications, the following four groups were used: 1) *VSN*: patients with moderate to severe visuospatial neglect, 2) *Mild*: patients with mild symptoms of VSN or visual inattention, 3) *Sub-clinical*: patients with sub-clinical symptoms of VSN or visual inattention, and 4) *No symptoms*: patients with no symptoms of VSN or visual inattention.

Functional Dependency (Studies I - IV)

Modified Rankin Scale (mRS; Bonita & Beaglehole, 1988).

The mRS is a disability scale shown to have acceptable intraobserver reliability and validity (Banks & Marotta, 2007; D'Olhaberriague, Litvan, Mitsias, & Mansbach, 1996; van Swieten, Koudstaal, Visser, Schouten, & van Gijn, 1988), however, the interrater reliability has been found to be modest (Banks & Marotta; Quinn, Dawson, Walters, & Lees, 2009). The mRS investigates patients' general functional activity level on a scale from 0 to 6. A score of 0 indicates no symptoms, 1 indicates no significant disability despite symptoms, 2 indicates slight disability but able to look after own affairs without assistance, 3 indicates moderate disability requiring some help, but able to walk without assistance, 4 indicates moderately severe disability being unable to walk or to attend to own bodily needs without assistance, 5 indicates severe handicap, totally dependent and requiring constant attention day and night, and 6 means deceased. The score on the mRS was dichotomized with a follow-up outcome score of ≤2 coded as functionally independent and >2 coded as dependent (Diener, 1998; Franke et al., 1996). The mRS was administered at three months (studies I - III), 2 years (Study II) and 7 years after the stroke (Study IV).

Frenchay Activities Index (FAI; Study IV)

The FAI (Holbrook & Skilbeck, 1983) was used as an outcome measure of engagement in social activities. The FAI is considered to be a valid, reliable and stroke-specific instrument

(Green, Forster, & Young, 2001; Post & de Witte, 2003; Schuling, de Haan, Limburg, & Groenier, 1993) which measures activity level related to four categories (domestic, leisure/work and outdoor activities). The FAI consists of 15 items asking for the frequencies with which an activity is performed. Each item is scored on a four point scale from 0 (low frequency) to 3 (high frequency). The FAI sum score is comprised of all the items added into a total score which ranges from 0 to 45. FAI scores close to 0 indicates inactivity and scores close to 45 indicates high activity. For the multivariate analyses the patients were categorized, as in previous studies (Jansen, Schepers, Visser-Meily, & Post, 2012; Patel et al., 2006), as inactive (FAI sum score ranging from 0 to15), moderately active (FAI sum score ranging from 16 to 30) and highly active (FAI sum score ranging from 31 to 45). The patients' level of activity was rated at a patient visit to the research nurse 7 years post-stroke.

Neurological Deficits and Localization of Brain Damage (Studies I - IV)

The patients were also examined with regards to neurological and functional deficits and localization of brain damage through the following procedures:

Scandinavian Stroke Scale (SSS; Boysen, 1992).

The SSS is a scale shown to have good reliability, which assesses neurological deficits acutely and at a follow-up (Lindenstrøm, Boysen, Christiansen, Hansen, & Nielsen, 1991). The scale is predicative of functional outcome (Christensen, Boysen, & Truelsen, 2005; Govan, Langhorne, & Weir, 2009). The SSS consists of an acute prognostic score and a long-term score for assessing neurological deficits acutely and at subsequent follow-ups. The max score for the total scale is 58. The SSS long-term score ranges from 0 (no physical functioning ability) to 48 (complete physical functioning ability) and consists of 7 sub-items. Each of the items arm- hand- and leg motor power on the affected side is rated on a five point scale (0, 2, 4, 5 and 6) where 0 equal paralysis and 6 equals normal strength. Orientation is scored on a four point scale (0, 2, 4 and 6) where 0 equal complete disorientation and 6 equals correct orientation for time, place, and person. Speech is rated on a four point scale (0, 3, 6 and 10) where 0 equals an ability to only express "yes/no" or less and 10 equals no aphasia. Facial palsy is scored on a two point scale where 0 equals present and 2 equals none or uncertain. Gait is rated on a five point scale (0, 3, 6, 9 and 12) where 0 equals bedridden or wheelchair bound and 12 equals the ability to walk 5 meters without aid. The SSS acute prognostic items (max score = 22) include scores on consciousness and eye movement in addition to the above described arm- and leg motor power. In Study I, the SSS long-term items were scored as the maximum stroke severity within the first 7 days post-stroke and a new score was assayed at the three month follow-up. In Studies II - IV the total SSS, scored as the maximum stroke severity within the first 7 days post stroke, was utilised. In addition, in Study III the total SSS assessed at three months was used.

Visual field deficit (VFD).

Occurrence of VFD was rated by a neurologist as being either present or absent using the conventional confrontation technique. In patients not assessed with regards to VFD the classification was based on a neurologist's retrospective examination of the information in the medical records. The numbers of patients classified retrospectively on VFD were 136 in Study I and 43 in Study II.

Localization of brain damage.

Patients' MRI/CT reports were reviewed to establish the sites of the brain-damages. Infarcts were classified as involving the right or left side of the brain, right or left cerebellum, and/or the brainstem. Previous infarcts or lesions of different origins were also recorded according to the above classification.

Lateralization of clinical neurological symptoms.

The neurological clinical symptoms described in the medical records were coded as either lateralized (right- or left sided) or nonlateralized symptoms.

Background Variables of Aetiology and Area of Vascular Supply (Studies III and IV)

Stroke aetiology.

The Trial of ORG 10172 in Acute Stroke Treatment (TOAST; Adams et al., 1993) was used to classify the etiologic subtypes of the strokes. The causal subtypes of this classification are small vessel disease, large vessel disease and cardioembolism. When no cause of stroke could be identified it was classified as being cryptogenic. Other causes and undetermined causes for the stroke were classified as "other". This classification was done by a neurologist (KJ) on the basis of face to face assessments within the first week (about 2/3 of the cases) and by reviewing the patients journals. If a classification was uncertain the judgment was done by two neurologists.

Vascular supply area.

The Oxford Stroke Classification (Bamford, Sandercock, Dennis, Burn, & Warlow, 1991) was used to assess the vascular origin of the stroke. This classification is considered to have satisfactory reliability and reasonably valid in establishing the localization and size of the infarction (Lindley et al. 1993; Wardlaw, Dennis, Lindley, Sellar, & Warlow, 1996). Strokes were classified as lacunar infarcts, total anterior circulation infarcts, partial anterior circulation infarcts, posterior circulation infarcts or infarcts with uncertain origin. This classification was done by a neurologist on the basis of face to face assessments within the first week (about 2/3 of the cases) and by reviewing the patients journals. If a classification was uncertain, the judgment was done by two neurologists.

Background Variables Assessed at the Long-Term Follow-up (Study IV)

Mini-mental State Examination (MMSE).

The MMSE (Folstein, Folstein, & McHugh, 1975) is a standardized brief screening instrument of cognitive functioning. This questionnaire is comprised of 11 items evaluating functioning in orientation, memory, attention, calculation, language and construction. Maximum score in the MMSE is 30 and values < 24 is a sign of cognitive impairment (Tombaugh & McIntyre, 1992). Tombaugh and McIntyre report that validity and reliability of the MMSE is satisfactory but that the validity of moderate to severe cognitive impairments is better than for mild impairment. The MMSE was rated at the patient's scheduled 7-year follow-up visit to one of two neurologists involved in the SAHLSIS.

Education.

At the long-term follow-up the patients' years of education was recorded. Education was dichotomized according to the norms of the Swedish educational system so that 9 years of education ("compulsory school") or less was classified as "low" and >9 years of education as "high".

Age.

Age at the long-term follow-up was included in the analyses.

Procedure

A research nurse administered the VSN assessments at baseline and at the three month follow-up. A neurologist on call assessed the patients with the Scandinavian Stroke Scale within one week after the admission to the stroke unit. A neurologist in the SAHLSIS project assessed the patients with the Scandinavian Stroke Scale and modified Rankin Scale at the three month follow-up. At two years after stroke a research nurse assessed the patients with regard to the modified Rankin Scale by means of telephone interviews. At 7 years the modified Rankin Scale and Frenchay Activities Index was administered by a research nurse whilst the Mini-mental State Examination was administered by a neurologist in the SAHLSIS project.

Statistical Analyses

Non-parametric statistical methods with an alpha level of $p \leq .05$ were used to analyse the data. Analyses of *k* samples were done by Kruskal-Wallis one-way analysis of variance by rank for continuous data and with Chi-square for categorical data. In two sample comparisons the Mann-Whitney U test was used for continuous data and Fisher's exact test for categorical data. Post-hoc two-sample comparisons were performed with the Bonferroni-Hochberg or Holms-Bonferroni corrections for multiple comparisons. Forward stepwise logistic regression analyses with an alpha level for inclusion of $p \leq .05$ and for exclusion of $p > .10$ were used in order to identify the most important predictors of functional dependency among the investigated variables. Only variables showing statistical significant differences at the univariate analyses were included in the logistic regressions. In Study II effect sizes were described in terms of the Pearson *r* and receiver operating characteristic (ROC) curves were used to graphically illustrate the sensitivity and specificity of the individual VSN variables. In Study III a "probability of superiority" effect size estimator, the PS_{dep} (Rusico & Gera, 2013; Vargha & Delaney, 2000), was calculated. Further, in order to estimate the rank order of the influences of the variables selected by the regression analysis in Study III, partially standardized logistic regression coefficients (b^*_a; Menard, 2004) were calculated. In studies III and IV Spearman's zero-order *Rho* and partial *Rho* correlations were calculated to explore the relationships of the scores of the individual symptoms with VSN severity at three months (Study III) and total sum score in the FAI at 7 years (Study IV). In Study IV multinomial stepwise logistic regressions with an alpha level for inclusion of $p \leq .05$ and for exclusion of $p > .10$ were used in order to explore the relative strengths of the predictors in distinguishing inactive patients from moderately and highly active as assessed with the FAI.

RESULTS

This section presents the main findings from the four studies. Following the main findings from each study some supplemental results are also described. The supplemental results related to Study I concern the pattern of recovery of the patients with lateralized inattention and how this pattern was related to functional outcome at three months. Analyses are also presented of the possible effects of 1) previous brain damages, 2) the retrospective examination for classification of inattention, and 3) the excluded patients. For Studies II-IV, the supplemental results are mainly further visualizations of the main analyses. An analysis of optimal cut-off levels was also included (Studies II). The end of this section is a summary of the combined results of studies II-IV.

Summary of the Empirical Studies

Study I

Substantial differences were found between the lateralized visual inattention (LVI) group and the general visual inattention (VI) and no visual inattention (NoVI) groups. Acutely the LVI group differed from the VI and NoVI groups by having more severe neurological deficits, left sided clinical symptoms, and right hemisphere damages (see Table 3). Also, more LVI patients were functionally dependent three months after stroke compared to both the VI and NoVI groups. At the three month follow-up, patients exhibiting LVI had more severe neurological deficits compared to both the VI and NoVI groups and patients with NoVI had a lower proportion of dependency compared to both the LVI and VI groups (see Table 4). The stepwise logistic regression analyses found that lateralized visual inattention was one of the significant predictors of functional dependency. In the total sample, patients with LVI were 5 times more likely to be dependent compared to patients with NoVI. RBD and LBD patients were also analyzed in two separate stepwise logistic regression analyses. These regressions showed that LVI was the most important predictor of dependency following right brain-damage. Patients with RBD and lateralized visual inattention were 27 times more likely to be functionally dependent three months after stroke compared to patients with NoVI. In LBD patients no significant relationship was found between symptoms of visual inattention and functional dependency.

Table 3

Results for the LVI, VI, and NoVI Groups on Neurological Symptoms, MRI/CT, and Functional Dependency at the Post-acute Stage.

Variables	LVI	VI	NoVI	*p* =
SSS	21/0-48*†	39/0-48‡	44 / 0-48	.000
Arm	1 / 0-6*†	6 / 0-6	6 / 0-6	.000
Hand	1 / 0-6*†	4 / 0-6	6 / 0-6	.000
Leg	3 / 0-6*†	5 / 0-6	6 / 0-6	.000
Orientation	6 / 0-6†	6 / 0-6	6 / 0-6	.000
Language	10 / 0-10†	10 / 0-10	10 / 0-10	.011
Facial	0 / 0-2†	2 / 0-2	2 / 0-2	.000
Walk	0 / 0-12*†	9 / 0-12‡	12 / 0-12	.000
VFD post-acutely	22 / 55%*†	10 / 27%‡	28 / 9.8%	.000
Clinical symptoms				
Non - asymmetric§	2 / 5%	9 / 24.5%	55 / 19%	ns
Right Sided	13 / 32.5%	18 / 48.5%	139 / 48.5%	ns
Left Sided	25 / 62.5%*†	10 / 27%	93 / 32.5%	.001
MRI/CT results				
MRI§	33 / 82.5%	32 / 86.5%	259 / 90%	ns
Normal MRI/CT	0	1 / 2.5%	23 / 8%	-
Acute Infarcts§	40 / 100%*†	30 / 81%	235 / 82%	.041
Left Hemisphere	12 / 30%	17 / 46%	110 / 38.5%	ns
Right Hemisphere	23 / 57.5%*†	8 / 21.5%	71 /24.5%	.000
Bilateral damage	2 / 5%	1 / 2.5%	6 / 2%	-
Brainstem§	3 / 7.5%	4 / 11%	33 / 11.5%	ns
Left Cerebellum	1 / 2.5%	1 / 2.5%	16 / 5.5%	-
Right Cerebellum	0	1 / 2.5%	24 / 8.5%	-
Non-acute infarcts	9 / 22.5%	11 / 29.5%	73 / 25.5%	ns
Left Hemisphere	2 / 5%	0	26 / 9%	-
Right Hemisphere§	5 / 12.5%	4 / 11%	26 / 9%	ns
Bilateral damage§	0	7 / 19%	10 / 3.5%	ns
Brainstem	0	1 / 2.5%	8 / 3%	-
Left Cerebellum	0	0	4 / 1.5%	-
Right Cerebellum§	3 / 7.5%	2 / 5.5%	1 / 0.5%	-
Functionally dependent	24 / 70.5%*†	11 / 34.5%‡	32 / 12.5%	.000

Values in Median/Range for ordinal data and number and percentage for nominal data.
* = $p \leq 0.05$ between the LVI and VI groups. † = $p \leq 0.05$ between the LVI and NoVI groups.
‡ = $p \leq 0.05$ between the VI and NoVI groups, §= scores of the LVI and VI groups are collapsed and compared to the NoVI group with Fisher's exact test. If significant, individual two-group comparisons were done. One patient (NoVI) was not assessed with the SSS, and six (4 NoVI, 1 VI, and 1 LVI) was not assessed on all sub-items.

Table 4

Results for the LVI, VI and NoVI Groups on Neurological Symptoms, MRI/CT, and Functional Dependency at the Follow-up Stage.

Variables	LVI	VI	NoVI	*p* =
SSS	39 / 9-48*†	46 / 19-48‡	48 / 11-48	.000
Arm	4 / 0-6†	6 / 0-6‡	6 / 0-6	.000
Hand	4 / 0-6*†	6 / 0-6‡	6 / 0-6	.000
Leg	5 / 0-6*†	6 / 4-6‡	6 / 0-6	.000
Orientation	6 / 4-6†	6 / 0-6‡	6 / 0-6	.018
Language	2010-03-10	2010-03-10	10 / 0-10	.ns
Facial palsy	2 / 0-2	2 / 0-2	2 / 0-2	.040
Walk	9 / 0-12*†	2012-03-12	2012-03-12	.000
VFD	3 / 25%	8 / 21.5%‡	16 / 5.5%	.000
Clinical symptoms				
Non-asymmetric	2 / 16.5%	2 / 5.5%	60 / 20%	-
Right sided	4 / 33.5%	18 / 48.5%	145 / 48%	ns
Left sided§	6 / 50%	17 / 46%	96 / 32%	.039
MRI/CT results				
MRI§	8 / 66.5%	30 / 81%	271 / 90%	.012
Normal MRI/CT	0	3 / 8%	21 / 7%	-
Acute Infarcts§	10 / 83.5%	32 / 86.5%	252 / 83.5%	ns
Left Hemisphere	4 / 33.5%	15 / 40.5%	120 / 40%	ns
Right Hemisphere§	6 / 50%	17 / 46%‡	73 / 24.5%	.001
Bilateral damage	0	0	7 / 2.5%	-
Brainstem	0	0	37 / 12.5%	-
Left Cerebellum	0	0	17 / 5.5%	-
Right Cerebellum	0	0	22 / 7.5%	-
Non-acute infarcts§	3 / 25%	9 / 24.5%	79 / 26%	ns
Left Hemisphere	1 / 8.5%	2 / 5.5%	25 / 8.5%	-
Right Hemisphere§	1 / 8.5%	3 / 8%	30 / 10%	ns
Bilateral damage	0	0	16 / 5.5%	-
Brainstem	0	1 / 2.5%	8 / 2.5%	-
Left Cerebellum	0	1 / 2.5%	3 / 1%	-
Right Cerebellum	1 / 8.5%	3 / 8%	2 / 0.5%	-
Functionally dependent§	9 / 82%†	15 / 48.5%‡	48 / 16.5%	.000

Values in Median/Range for ordinal data, and number and percentage for nominal data.
* = $p \leq 0.05$ between the LVI and VI groups.† = $p \leq 0.05$ between the LVI and NoVI groups.
‡= $p \leq 0.05$ between the VI and NoVI groups.§ = LVI and VI groups are collapsed and compared to the NoVI group with Fisher's exact test. If significant, individual two-group comparisons were done.18 participants were not assessed with the SSS (11 NoVI, 6 VI, and 1 LVI)

Supplemental results not included in the manuscript of Study I.
At the three month follow-up after the stroke, the patients with LVI at the acute stage were divided into three different sub-groups according to the recovery of visual inattention. One subgroup still had LVI (n = 10), another group improved to VI (n = 12), and a third group recovered to NoVI (n = 16). No statistically significant differences were found between these three groups concerning acute neurological deficits and damage localisation. With regards to functional dependency, those who had recovered to NoVI differed from the two other groups by having a higher proportion of independent patients (Fisher's exact, $p < .001$). However, this group which had recovered to NoVI differed from the group of patients who had NoVI both acutely and at follow-up by showing a higher proportion of functionally dependent patients (Fisher's exact, $p = .010$).

The retrospective examination of the medical records in patients not tested on the Star Cancellation test led to the inclusion of 15 more patients with acute LVI, 5 patients with acute VI and 22 patients with NoVI. At follow-up three more patients with LVI, 6 patients with VI and 13 with NoVI were identified. Additional statistical analyses were run without the patients identified through the medical records. The outcomes from these analyses were compared to the results described above. The additional analyses showed the same patterns of statistically significant group differences. However, the inclusion of the patients based on the medical records resulted in more distinct group differences (i.e. lower p values). A larger proportion of patients with LVI were observed after inclusion based on the medical records, especially for the patients with LBD (see Table 5).

Table 5

Number of Patients with LVI, Identified by SCT and by Medical Records at the Post-acute Stage, and the Localization of Brain-damage

	SCT only	Medical records	Total
Right brain damage	16	7	23
Left brain damage	4	8	12
Total	20	15	35

Abbreviation: SCT = Star Cancellation test

For the patients with LVI who had both an acute- and a non-acute brain lesion it was found that when the lesions were confined to one hemisphere, it led to inattention lateralized to the contralesional side (see Table 6). However, for the patients with signs of a non-acute brain lesion in the hemisphere opposite the acute lesion, the symptoms of visual inattention could be ipsilesional relative to the acute infarct. For example, three out of four patients with an acute left infarct and a non-acute right infarct exhibited such an ipsilesional left sided inattention. Table 7 provides additional information about all patients in the LVI group who had signs of both acute and non-acute lesions, also including lesions to the brainstem and cerebellum. The results show that patients with ipsilesional inattention still had contralesional neurological clinical symptoms consistent with the acute infarct. One on the patients with acute LBD and non-acute RBD had left LVI acutely, but right LVI at follow-up.

Table 6

Localization of Acute and Non-Acute Brain- damages in Patients with LVI at the Post-acute Stage

MRI/CT Results	Right LVI	Left LVI
LBD (*n* = 12)		
LBD only*	8	0
Acute LBD + non-acute RBD‡	1	3
RBD (*n* = 23)		
RBD only**	0	21
Acute RBD + non-acute LBD	1	1

Abbreviations: LVI = lateralized visual inattention, LBD = left brain damage, RBD = right brain-damage. * = acute LBD only or acute and non-acute LBD in combination.
** = acute RBD only or acute and non-acute RBD in combination.

Analysis of excluded patients.

Of the total 375 patients, 11 could not be classified with regards to the occurrence and type of visual inattention and were thus excluded from the analysis. These 11 patients scored significantly inferior on total SSS score and on all sub-items of the SSS, and were more often functionally dependent three months after the stroke compared to the 364 included patients. However, with regard to laterality of clinical symptoms and MR/CT results, there were no significant differences. At follow-up 7 out of 357 patients could not be classified with regard to occurrence and type of visual inattention. Compared to all the included patients, the 7 excluded were significantly more often functionally dependent three months after stroke.

Table 7

Lateralized Inattention and Neurological Symptoms in LVI Patients with Acute and Non-Acute Brain-damages

Patients	Side of inattention SCT	Clinical neurological symptoms	MRI/CT	
			Acute infarcts	Non-acute infarcts
Ipsilesional inattention				
1	Right	Left sided	RBD	LBD
2	Left	Right sided	LBD	RBD
3	Left	Right sided	LBD + BS	RBD
4	Left	Right sided	LBD	RBD
Contralesional inattention				
5	Left	Left sided	RBD	RC
6	Left	Left sided	RBD	LBD
7	Left	Left sided	RBD	RC
8	Left	Right sided	BS	RBD
9	Right	Right sided	LBD	RBD + RC

Abbreviations: SCT = Star Cancellation test, RBD = right brain-damage, LBD = left brain-damage BS = Brainstem, RC = right Cerebellum

Study II

All three core symptoms of visuospatial neglect (omissions, asymmetry of omissions and ipsilesional bias) in this study showed strong relationships with functional dependency three months and two years after stroke onset (see Table 8). Moreover, strong associations were observed between functional dependency and the VSN related symptom of slow processing speed and also between dependency and neurological deficits. The stepwise logistic regressions identified spontaneous right capture of attention in orientation as the only significant predictor of dependency three months after stroke. Patients who began their searches, on average, in the second column from the left were 44.5 times more likely to be dependent three months after stroke compared to patients who began the tests in the first column from the left. Slow processing speed, defined as time used per identified letter on the letter cancellation task, was the only significant predictor of dependency two years after stroke. Patients who used 4 seconds per identified target letter were 9.8 times more likely to be dependent two years after stroke compared to patients who used 2 seconds per identified letter.

In order to further illustrate the predictive value of the core symptoms of neglect and the related symptoms of neglect, these variables were plotted in receiver operating characteristic (ROC) curves. A ROC curve is a graphical plot of sensitivity versus specificity used to differentiate between optimal and suboptimal models of observed data. Figure 2 shows the close relationships between the tested variables and their sensitivity and specificity in predicting functional dependency. The term “sensitivity” relates to the proportion of observed dependent patients (true positives) each measure is able to identify.

Table 8

Scores on the Acute Measures for Functionally Dependent and Independent Patients at Three Months and Two Years After Stroke

	Functional dependency					
	3 months			2 years		
	Dependent (n=16)	Independent (n=71)	r/OR	Dependent (n= 17)	Independent (n= 70)	r/OR
VSN variables						
Omissions (average %)	23.6(3.3-41)	1.9(.6-4.3)**	.47	4.7(2.1-34.5)	2.4(.6-5.4)*	.28
CoC (average)	.05(.01-.35)	0(0-.01)**	.46	.03(0-.30)	0(0-.01)*	.33
Start column (average)	2(1.5-2.6)	1(1-1.2)**	.54	1.6(1.1-2.6)	1(1-1.2)**	.42
VSN related variables						
Repetitions (average %)	0(0-5.9)	0(0)*	.29	0(0-5.2)	0(0)[ns]	.21
Seconds per identified letter on the LC[a]	4.1(2.5-10)	2(1.6-2.3)**	.54	3.9(2.4-9.1)	2(1.6-2.3)**	.52
Omissions on SCT-B (average %)	50(24.5-70.8)	7.4(0-33.3)**	.43	50(29.6-66.2)	5.6(0-31.5)**	.47
Variables of neurological deficits						
SSS[b]	31(24-49)	55(51-58)**	.46	43(24.5-49)	55(51-58)**	.43
VFD	5 - 31.3%	4 - 5.6%*	7.61[c]	4 - 23.5%	5 - 7.1%[ns]	4.00[d]

VSN - Visuospatial neglect; CoC - Center of Cancellation; SCT-B - Star Cancellation test B; SSS - Scandinavian Stroke Scale; VFD - Visual Field Deficit; r – Pearson r; [a]Dependent, 3 months (n=14) and 2 years (n= 16); Independent, 2 years (n= 69); [b]Dependent, 3 months (n= 15) and 2 years (n= 16). [c]95% CI = 1.77-32.83, p= .007; [d]95% CI = .94-16.94, ns; * = p≤ 0.01, ** =p≤ 0.001. Values are given as: median (Q1;Q3, range 25th to 75th percentiles).

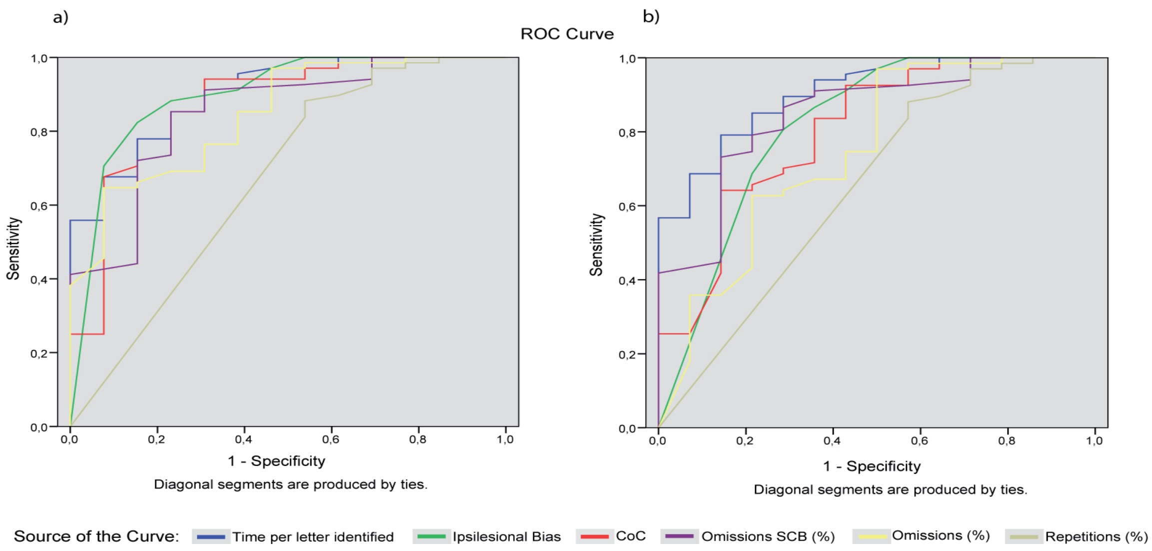

Figure 2. ROC curves of the relationship between functional dependency three months (a) and two years (b) after stroke and different sub-symptoms and symptoms related to VSN. The larger the area under the curve, the better the measure is at predicting dependency.

That is, if a score in one of the measures has a sensitivity of 0.8 using this score as a cut-off correctly identifies 80% of the truly dependent patients. The X-axis values represent an inverted scale of specificity (1- specificity). Thus, in this inverted scale, a low score describes the proportion of observed independent patients (true negatives) each measure is able to identify. That is, if a score in one of the measures has a 1-specificity of 0.2 using this score as a cut-off correctly identifies 80% of the truly independent patients. Thus, when sensitivity and 1-specificity are plotted in the same graph, a theoretical point in the upper left corner would represent an optimal combination of sensitivity and specificity. The size of the area under the curves is positively related to each measure's ability to predict dependency. According to Figure 2, and in agreement with the results of the logistic regressions, start column of search and time per identified letter, were the measures with the best combination of sensitivity and specificity. Both graphs also indicate that visual processing speed in terms of time per cancellation and the two measures of laterality of inattention all have strong relationships with functional outcome. The weakest predicative information is indicated for repetitions in target detection and number of omissions.

Supplemental results not show in the manuscript for Study II.

Further analyses were made for the prediction of functional outcome at the three month follow-up. These analyses included all patients with complete data on the variables time per letter cancellation and average start column and with complete data on dependency at three months. The three patients with a recurring stroke within the three month follow-up were excluded. Using the coordinates of each individual ROC curve a cut-off score was obtained. At the selection of a cut-off score, we tried to obtain the best overall prediction rate and at the same time maintain clinically meaningful information by keeping the level of sensitivity and specificity of dependency not lower than 70%. A cut-off score of 3.46 seconds for the time per cancelled letter was selected and this yielded a total correct prediction of 89.9% (sensitivity = 72.2% and specificity = 94.4%). For average start column a cut-off score of 1.5 was selected resulting in a total correct prediction rate of 85.4% (sensitivity = 77.8% and specificity = 87.3%).

Figure 3 illustrates the proportion of dependent and independent patients identified by the cut-off levels described above. Figure 3 show that 62 patients (70%) of the total sample had scores at or below the cut-off levels in both variables (≤ 3.46 sec. and start column ≤ 1.5). Of these patients 95% were correctly identified as independent according to the mRS cut-off level. Also, Figure 3 shows that 13 patients (15%) of the sample had scores above cut-off in both variables. Of these patients 92% were correctly identified as dependent. Of the total sample, 14 patients (16%) scored above cut-off in only one of the two variables. Of these patients about 36% was correctly identified by the start column and about 64% was correctly identified by the time per cancelled letter.

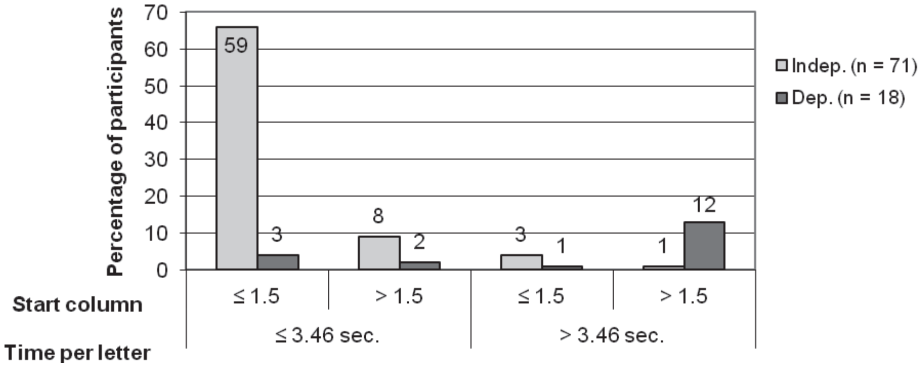

Figure 3. Dependency at three months after stroke and the relationship between time used per identified letter in the LC test and start column of searches. The numbers on top of each bar denotes the actual number of patients.

Study III

Table 9 shows the odds ratios, 95% confidence intervals and *p*-values for the regression of scores in the VSN assessment at three months after stroke and dependency at the same time. Before the inclusion of any of the variables, the model had a by chance classification accuracy of 77.8%. In step one of the regression SCT-B was found to be a significant predictor and at step two (final step) both SCT-B and start column were found to be significant. The most influential predictor of the two, as estimated by the b^*_a, was ipsilesional bias. The overall accuracy rates of correct classifications were 86.7% after step one and 92.2% after step two.

Table 9

Regression of Scores at Follow-up and Functional Outcome at Follow-up

	Odds ratio	CI 95%	*p* =
Step 1			
SCT-B	1.077	1.044 - 1.112	.001
Step 2			
SCT-B	1.058	1.022 - 1.094	.001
Start column	11.675	1.536 - 88.747	.018

The dependent group was the reference category in the regression.
SCT-B = Star Cancellation Test -B. The by chance accuracy of classification was 77.8%.

Table 10 shows the level of recovery of patients, post-acutely to follow-up, in the three groups *VSN*, *Mild*, and *Sub-clinical* (in total 51 patients). In the acute VSN group (n=13) only one patient recovered to no symptoms, one patient had sub-clinical VSN and 7 patients (54%) had mild VSN. Of these acute VSN patients, 4 (31%) still exhibited moderate to severe VSN three months after stroke onset.

In the mild group (n = 17), 7 patients (41%) recovered to no symptoms and 6 patients (35%) had sub-clinical symptoms. In this group 4 patients (24%) still showed mild symptoms.

In the sub-clinical group (n = 21), 8 patients (38%) recovered to no symptoms. In this group 7 patients (33%) still had sub-clinical symptoms and 6 patients (29%) had mild symptoms at follow-up.

Table 10

Change in VSN Classification From Acute to Follow-up Assessment

		Acute		
		VSN (n = 13)	Mild (n = 17)	Sub-clinical (n = 21)
Follow-up	VSN (n = 4)	4	-	-
	Mild (n = 17)	7	4	6
	Sub-clinical (n = 15)	1	6	7 (+1)[a]
	No symptoms (n =16)	1	7	8

VSN = moderate to severe VSN. Mild = mild VSN (acute n = 14; follow-up n = 14) and mild visual inattention (acute n = 3; follow-up n = 3). Sub-clinical = sub-clinical VSN (acute n = 14; follow-up n = 8) and sub-clinical visual inattention (acute n = 7; follow-up n = 7).[a] = one patient classified as having no symptoms acutely.

In summary, of the 51 patients classified as having at least sub-clinical symptoms at the post-acute stage, 16 (31%) had recovered to no symptoms. All of these patients were from the mild or sub-clinical group, excepting one patient from the VSN group. Some recoveries (to a lower level) were observed in 14 patients (27%). No recoveries were observed in 21 patients (41%).

Supplemental results not included in the manuscript of Study III.

Figure 4 illustrates the improvement rates of the VSN and mild groups separately for the lateralized and nonlateralized symptoms of VSN. Overall, marked improvements are observed for the VSN group. However, despite the substantial recovery, the tendency is that their follow-up scores are worse than the post-acute scores of the mild group. Thus, as a group the VSN patients still exhibit impaired performances at follow-up.

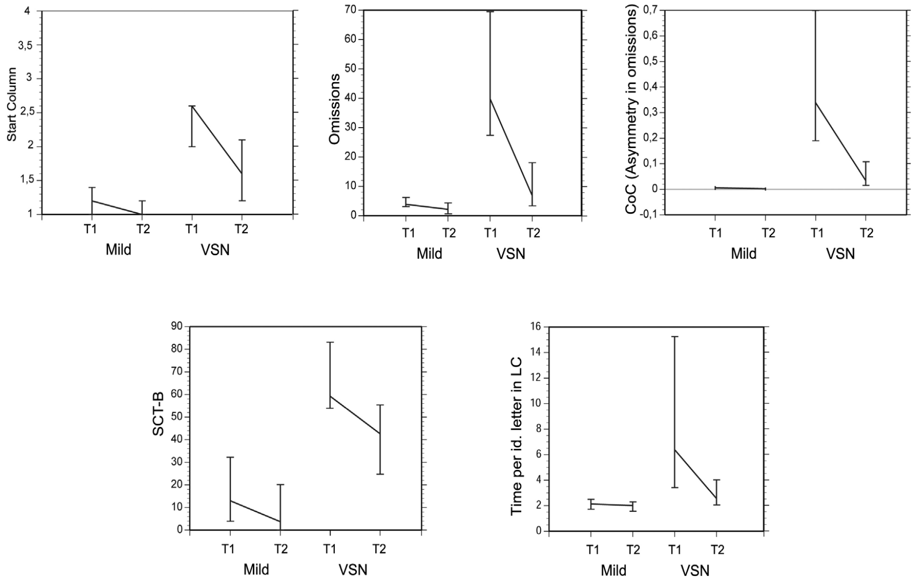

Figure 4. Performance improvements of the VSN and Mild groups from post-acute (T1) assessment to three months after stroke (T2) in each VSN variable

Study IV

Table 11 shows the odds ratio, 95% confidence interval and *p*-value for the predictors that were found to be significant in the regression analysis of post-acute scores for VSN symptoms and functional dependency at 7 years after stroke. As can bee seen from block two in Table 11 time per identified letter is found to, over and above that of stroke severity alone, predict dependency at 7 years. However, stroke severity is also a significant predictor of dependency.

Table 11

Prediction of Functional Dependency at 7 Years

	Odds ratio	CI 95%	*p* =
Block 1			
Scandinavian Stroke Scale	0.915	0.859 - 0.974	.005
Block 2			
Scandinavian Stroke Scale	0.933	0.875 - .994	.032
Time per identified letter in LC	3.550	1.326 - 9.503	.012

LC = Letter Cancellation Test.

Table 12 shows the odds ratio, 95% confidence interval and *p*-value for the predictors that were found to be significant in the regression analysis of post-acute scores for VSN symptoms and level of engagement in social activities at 7 years after stroke. The regression analysis showed that the Scandinavian Stroke Scale and time per identified letter in the LC could significantly distinguish between moderately active and inactive patients 7 years after stroke. Age was not found to add any further significant information with regards to this distinction between moderately active and inactive patients.

Table 12

Prediction of Activity Level at 7 Years After Stroke

	Odds ratio	CI 95%	p =
Moderately active (n = 25) vs. inactive (n = 9)			
Age	0.824	0.647 - 1.050	.117
Scandinavian Stroke Scale	1.106	1.012 - 1.209	.027
Time per identified letter on the LC	0.296	0.092 - 0.957	.042
Highly active (n = 20) vs. inactive (n = 9)			
Age	0.773	0.602 - 0.992	.043
Scandinavian Stroke Scale	1.073	0.984 - 1.169	.111
Time per identified letter on the LC	0.110	0.023 - 0.525	.006

LC = Letter Cancellation Test

In distinguishing between the highly active and the inactive groups, age and time per identified letter on the LC were found to be significant predictors. A negative relationship was observed between time per identified letter and the odds of being in the highly active group compared to the inactive group. Thus, slow processing speed early after stroke is an independent predictor in differentiating dependent from independent patients and inactive from moderately and highly active patients at 7 years after stroke.

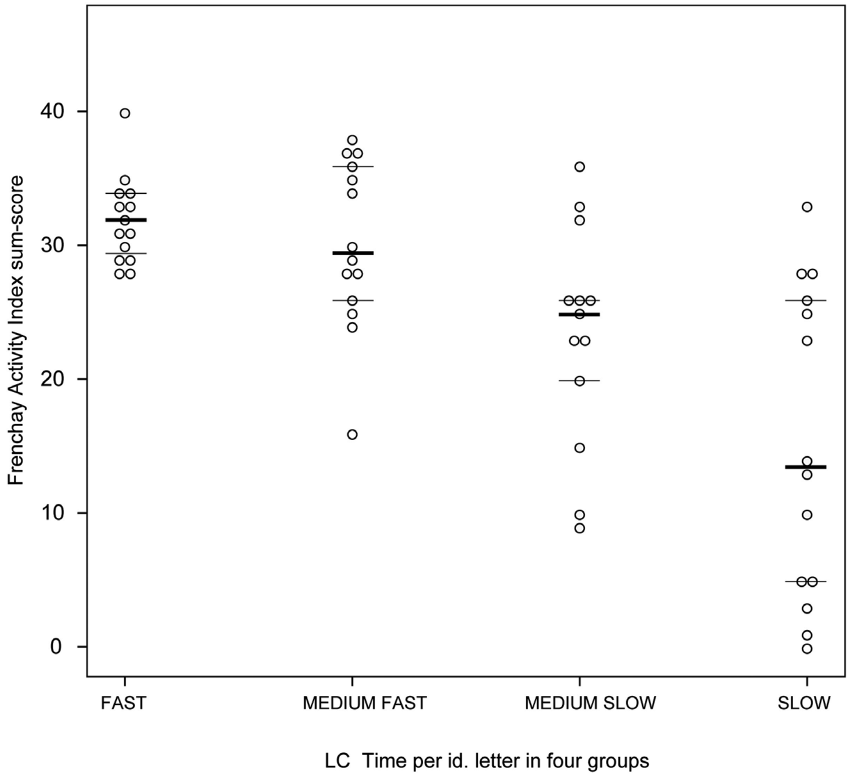

Figure 5. Total sum score of the Frenchay Activities Index at 7 years post stroke per the quartile groups in time per identified letter in the Letter Cancellation test post-acutely. The bold lines represent the median and the standard lines represent the 25th and 75th percentile of each quartile group.

Supplemental results not included in the manuscript of Study IV.

Figure 5 further illustrate the observed relationship between processing speed and activity level. A marked negative realtionship seems to exist between the two measures.

That is, as the time used per identified letter in the assessment early after stroke increases, the probability of being highly active 7 years after stroke decreases. However, as can be seen by the dots marking individual patients, the variability in activity level, especially for the "slow" group is large.

Figure 6 shows how one of the groups, either the inactive or the highly active, can be predicted by the processing speed measure. That is, an average post-acute score of above 2.3 seconds per identified letter indicates a very low probability of being highly active in the long-term after stroke. Likewise, a score below 2.3 seconds indicates a very low probability of being inactive at 7 years after stroke.

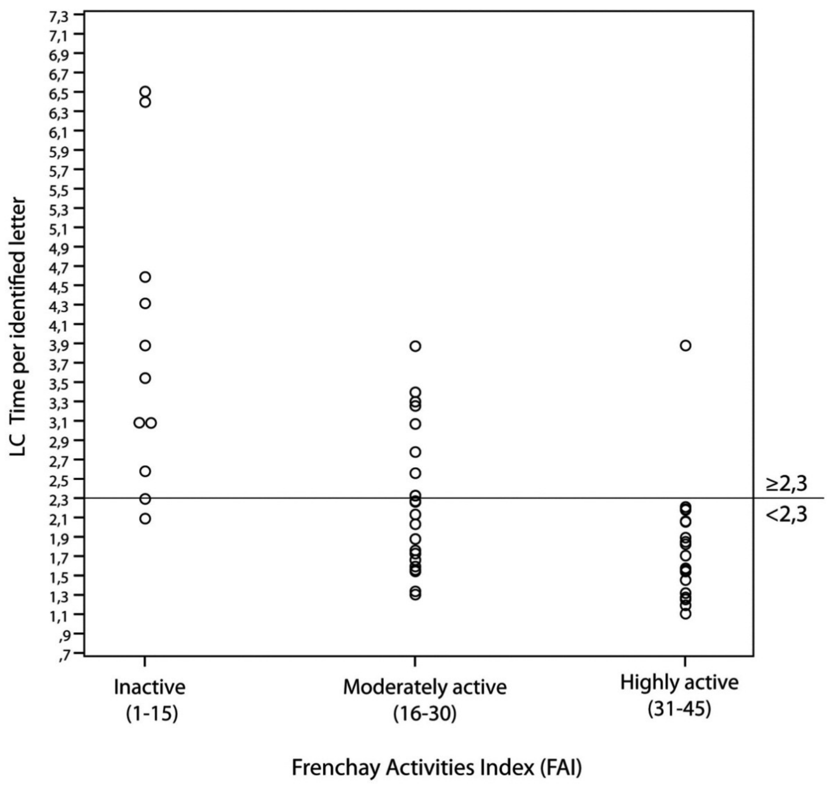

Figure 6. The post-acute time per identified letter in the Letter Cancellation test per classification in the Frenchay Activities Index divided into inactive, moderately active and highly active patients at 7 years after stroke.

Summary of Studies II –IV

In studies II – IV several lateralized and nonlateralized symptoms of VSN at an early stage after stroke were analyzed to asses their relative abilities to predict functional outcomes at different long-term follow-up sessions post-stroke. Figure 7 shows the variables that were selected at the final block or step in the multivariate logistic regression. Figure 7 also depicts the odds ratios and confidence interval for the odds ratios for the significant predictors of functional dependency at 3 months, 2 years and 7 years after the stroke and the odds ratios and confidence interval for predictors of social activities at 7 years after the stroke. The scales of the different predictor variables are adjusted at the computation of the odds ratios in order to obtain positive coefficient for all variables. That is, all confidence intervals of the significant variables is located at the same side of “1” in Figure 7. For the shortest interval (three months after stroke) the post-acute variable start column (the spatial location of the start of cancellations in the search tasks) was the only significant predictor of dependency at the final step of the multivariate analysis. Processing speed (time per identified letter) at the post-acute stage was found to independently predict dependency at two and seven years after stroke. Stroke severity early after stroke was also found to be a significant predictor of dependency at 7 years after stroke. Post-acute processing speed and stroke severity could distinguish between inactive and moderately active patients at 7 years whilst processing speed and age differentiated between inactive and highly active patients.

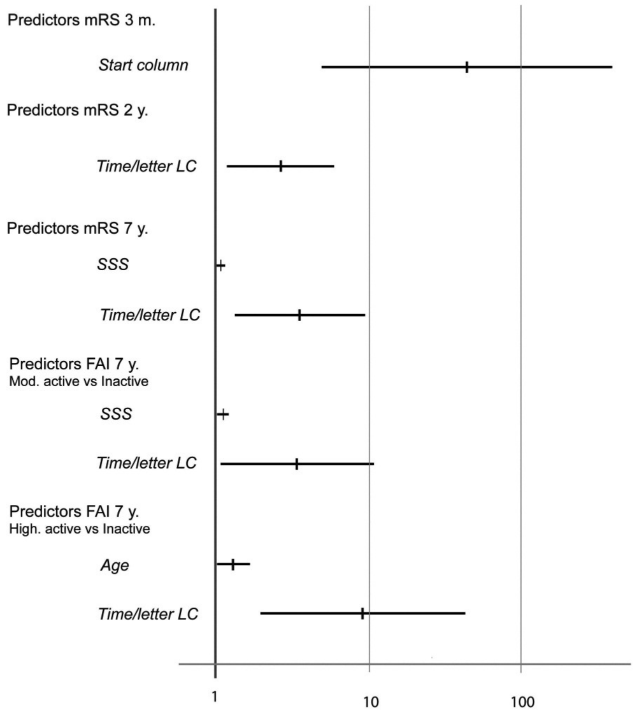

Figure 7. Odds ratios and 95% confidence intervals for the significant predictors of dependency at three months, two years and 7 years and for level of engagement in social activities at 7 years after stroke. m = months. y = years. mRS = dichotomized modified Rankin Scale with scores > 2 indicating dependency. Time/letter LC = time per identified letter in the Letter Cancellation task. SSS = Scandinavian Stroke Scale. FAI = Frenchay Activities Index. Mod = moderately. High = highly. The odds ratios of age and time per identified letter are inverted in order to be represented as odds ratios above 1.

These results indicate that for the relative short-term outcome a post-acute lateralized VSN symptom is important in predicting outcome (bias in start column). The predicative ability of this lateralized symptom seems to diminish over time and instead increased importance is demonstrated for general processing speed (a nonlateralized symptom) at the post-acute stage.

The prospective design of the studies allows description of patterns of change in levels of functional dependency described by mRS scores 0 to 5, with scores at three month, two years and seven years afte stroke. Figure 8 depicts the four quartile groups with regard to performance at the post-acute stage on time per cancelled letter in the LC test (LC Fast, LC Medium Fast, LC Medium Slow, and LC Slow). For each quartile group the proportion of patients at the separate scale scores in the mRS are shown - at three months, two years and seven years. Figure 8 shows that in the two groups that performed faster than the median at the post-acute stage, none of the patients, at any of the follow-ups, had a mRS score above 2. This means that the patients at least are able to carry out all usual duties and activities (mR≤2). A tendency of improved mRS scores can be seen in these groups over time. In the medium slow group a slight improvement in mRS scores is indicated between three months and two years, whilst a tendency towards decline seems to happen from two to seven years after stroke. In the slow group a decline is shown. At three months after stroke about 35% of these patients were to some extent dependent on others (a mRS score >2) in activities of daily living, whilst at 7 years about 55% were dependent on help.

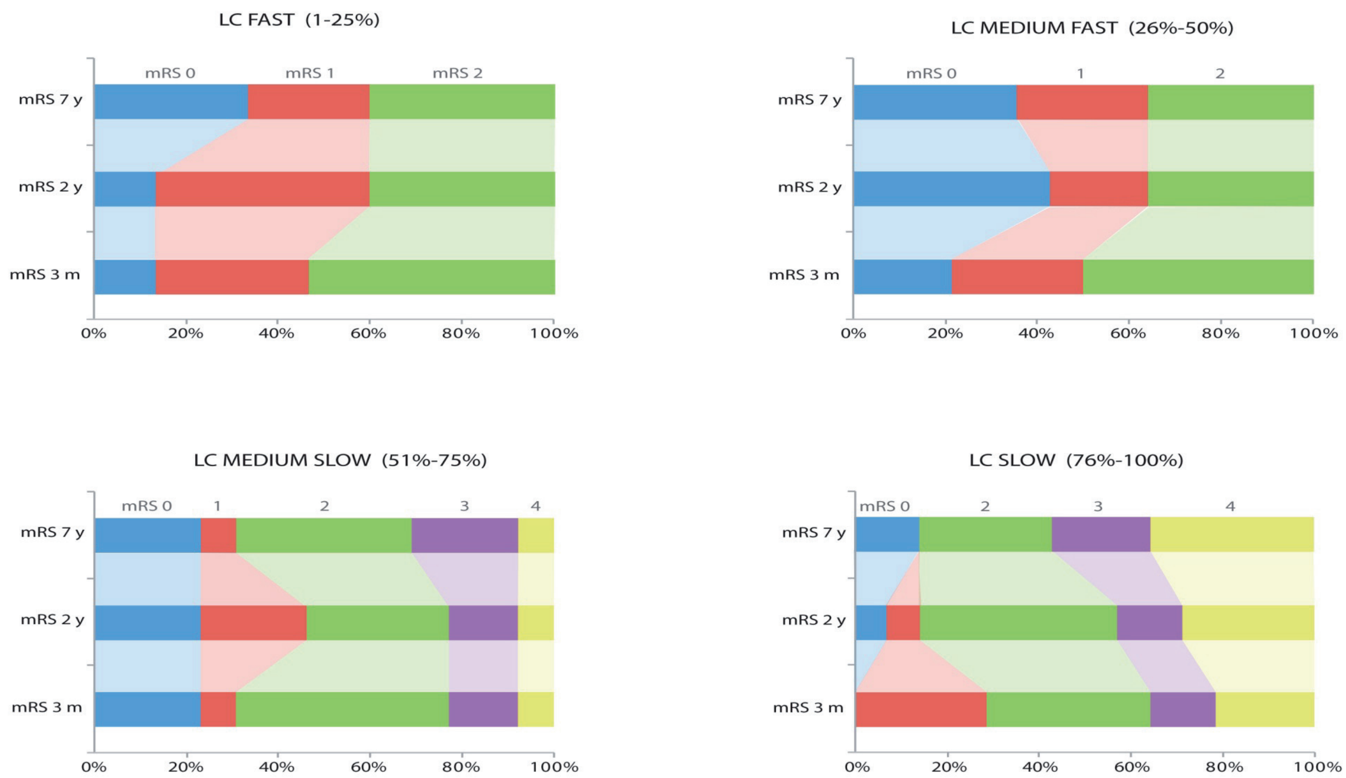

Figure 8. Changes in proportion of patients classified at each scale score in the mRS at three months, two years and 7 years per quartile group performance in time per identified letter in the Letter Cancellation test post-acutely.

Figure 9 illustrates the overall direction of change in mRS scores from the 3 month assessment to the 7 years assessment. The figure shows the proportion of patients who had a change between these two occasions in terms of:

- Worse; a change of at least one score in a negative direction (for example from score 2 to score 3)
- Stable; no change in score
- Improved; a change of at least one score in a positive direction (for example from score 3 to score 2)

The proportion of patients with change (Worse, Stable or Improved) are shown for each of the four quartile groups based on the post-acute scores on time per identified letter in LC test (LC Fast, LC Medium Fast, LC Medium Slow, and LC Slow). Figure 9 indicates that patients with slower processing speed early after a right hemisphere stroke, compared to faster patients, tend to show a negative pattern of change with regards to functional dependency.

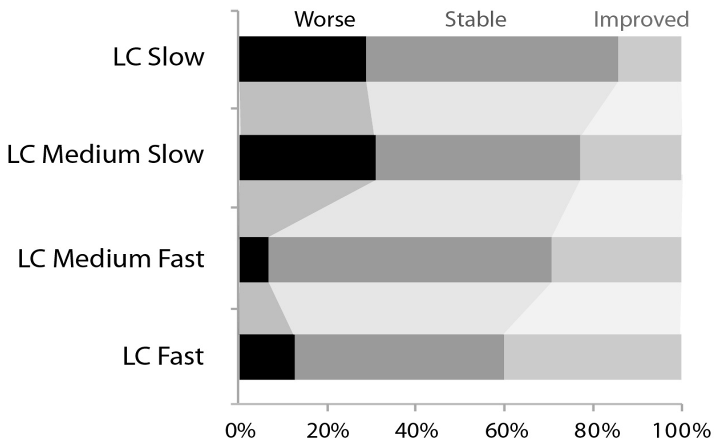

Figure 9. Overall direction of change (Worse, Stable and Improved) in the mRS from three months to 7 years after stroke per post-acute quartile group in the time per identified letter in the Letter Cancellation test

In summary, the results from studies II-IV provide strong support for the importance of processing speed at the post-acute stage as a predictor of long-term functional outcome post-stroke.

DISCUSSION

VSN in Relation to Functional Outcome After Stroke

The substantial differences demonstrated between patients with lateralized, nonlateralized and no visual inattention in Study I support previous findings that VSN is related to more severe neurological symptoms and that acute VSN predicts functional dependency. A strong relationship between VSN and functional outcome vas observed for the patients with a right hemisphere stroke, but not for those with a left sided stroke. In Studies II - IV, the spatially lateralized and nonlateralized symptoms of visuospatial neglect after right hemisphere strokes showed significant relationships with functional dependency. Especially strong associations were observed for slow processing speed and, to a lesser degree, spontaneous ipsilesional bias of attention. Slow processing speed early after stroke could differentiate inactive patients from moderately and highly active patients in social activities 7 years after stroke. The results presented here indicate that the symptoms associated with VSN that predict functional dependency and level of activity for up to 7 years corresponds to the components considered to be important in the theorized mechanisms underlying severity and persistency of VSN (Corbetta & Shulman, 2011; Kinsbourne, 1993; Robertson, 1993, 2001)

VSN and Functional Dependency within the First Three Months after Stroke

In Study I, possible group differences were studied in order to analyse if recovery from VSN was associated to functional dependency at follow-up. In the patients who improved from lateralized inattention (i.e. from VSN) to no inattention a smaller proportion was dependent at three months compared to the group of patients who had persisting symptoms of lateralized inattention. However, these patients who recovered to no inattention still had a higher proportion of patients who were dependent compared to the patients who had no inattention at both assessments (post-acute and follow-up). Similar results were observed for the patients who recovered from lateralized inattention to nonlateralized inattention. This finding suggests that symptoms of asymmetric inattention at an early stage after stroke provide prognostic information about dependency. Thus, the observations imply that patients with no signs of visual inattention, but with a history of asymmetric neglect, may have a higher risk of functional dependency relative to patients without a history of asymmetric neglect. The same pattern was observed for patients with a history of asymmetric neglect and signs of nonlateralized inattention at a later stage. However, it should be noted that in Study I visuospatial neglect was classified based on asymmetry of omissions in one test only. This is important as the assessment of VSN, especially at the three month follow-up, might not have been sensitive enough to identify subtle sub-clinical symptoms of lateralized or nonlateralized inattention that could have clinical importance (Mattingly, Bradshaw, et al., 1994; Rengachary et al., 2009; Webster et al., 1995). Also, due to the possibility of undetected symptom of VSN, the observed pattern of recovery from VSN might be somewhat misleading. Further, in Study I a qualitative classification of VSN was utilized. Therefore, the results could not inform as to which of the different sub-symptoms of neglect that might be important in relation to dependency.

In Study II, which included several different continuous measures of lateralized and nonlateralized symptoms related to VSN, post-acute ipsilesional bias was selected as a significant predictor of dependency at three months. In Study III similar analyses were made between functional dependency and the individual measures of neglect and processing speed, but this time only for the scores obtained at *three months post stroke.* It was found that of these predictors the strongest correlates of dependency were processing speed and ipsilesional bias. In Study III it was also indicated that, from the post-acute stage to three months after stroke, the symptoms of lateralized performance (ipsilesional bias and asymmetry of omissions) showed more favourable recovery than the nonlateralized symptom of processing speed.

It should be noted that in the univariate analyses regarding dependency at three months, the three proposed key symptoms of VSN (omissions, asymmetry in omissions, and ipsilesional bias) were significantly related to outcome. Also, the ROC curves in Figure 2a indicated that these symptoms were rather similar in their ability to predict the three month outcome. Moreover, in the regression analyses predicting functional outcome at three months, the 95% confidence interval of the ipsilesional bias variable was large. As such, with regard to the symptoms in the proposed core components of VSN, it is difficult to draw any firm conclusions of the relative importance of these symptoms.

In line with previous studies the results thus indicate that, despite improvements in the test performances, both lateralized and nonlateralized attentional symptoms are related to functional outcome within the first months after a right hemisphere stroke (Kettunen et al. 2012; Mattingley, Bradshaw, et al., 1994; Robertson, Ridgeway, Greenfield, & Parr, 1997; Webster et al., 1995). Furthermore, the current findings indicate that knowledge regarding the history and the progression of neglect symptoms at an early stage (i.e. the initial weeks) post-stroke could provide important prognostic information.

VSN as Predictor of Long-term Functional Outcome

Overall, the results presented in this thesis provide strong and consistent support for visual processing speed as an important independent predictor of long-term functional outcome following right hemisphere stroke. After controlling for overall stroke severity, processing speed was still an independent predictor of functional dependency at 2 years after stroke (Study II) and of dependency and social activities at 7 years post-stroke (Study IV).

The negative role of VSN and symptoms related to this phenomenon in long-term outcome after stroke has been reported in previous studies (Jehkonen et al., 2000, 2006; Kotila et al, 1986; Nijboer, van de Port, et al., 2013). Young, Bogle, and Forster (2001) reported results showing that having neglect within the first 6 weeks following a stroke was one of the significant predictors of social outcome at one year after stroke. Social activity was measured by a dichotomized Frenchay Activities Index and neglect was assessed by a cancellation test. Jehkonen and colleagues (2007) investigated recovery in neglect and in level of social activities during the first year after stroke. The patients with fluctuating improvement from neglect, compared to patients with continuous and more complete improvement, were found to show less recovery in level of social activity, especially for the first 6 months after stroke. This study was described in more detail in the background of this thesis.

Lateralized and Nonlateralized Symptoms of VSN as Predictors of Long-term Outcome

Only few studies have analyzed the relationship between functional outcome and the specific symptoms related to VSN in the same sample (Kettunen et al., 2012; Mattingley, Bradshaw, et al., 1994; Webster et al., 1995). Kettunen and coworkers found a significant correlation between ipsilesional bias and basic ADL in right hemisphere patients when both measures were assessed within 10 days from stroke onset. At a 6 month follow-up of the patients with baseline VSN, some residual ipsilesional bias was observed whereas marked improvements in target omissions and ADL were found. However, no relationship between ipsilesional bias and ADL was found at the follow-up. In the studies by Mattingley, Bradshaw, et al. and Webster and colleagues, residual symptom of ipsilesional bias was observed in absence of asymmetry of omissions. In Webster and coworkers' report the occurrence of this residual bias was associated with more errors in a wheel-chair maneuvering task at about 5 months after stroke and Mattingley, Bradshaw, et al. suggested that the persisting subclinical symptom might be one reason for the inferior functional outcomes often seen in patients with VSN early after stroke. The above examples and the results of Study III indicate that within the first months following a stroke ipsilesional bias seems to be associated with measures of functional outcome.

In a cross-sectional study at one year after stroke, Verhoeven et al. (2011) investigated the associations between cognitive functions and several measures of quality of life in 92 stroke patients. In this report social participation and functional independence showed the strongest relationships with cognitive functions. However, when controlling for motor impairments and demographic variables in multivariate regressions, the cognitive functions did not add predictive value to the differentiation of dependency, while for the more complex functions of social participation, unique influence was found for overall cognitive functioning. For the specific cognitive domains, attention and psychomotor function were found to add predictive value to that of motor impairment, gender, and education.

Robertson, Ridgeway, et al. (1997) assessed 47 right hemisphere damaged patients with measures of sustained attention and motor and functional status at two months and two years after stroke. At two years after stroke a test of hand dexterity and a test of mobility were also administered. First, the authors analyzed the correlations between the functional status at two years and the sustained attention measures both at two months and at two years. The number of significant correlations was calculated. The total number of significant correlations for outcome at two years was 46%. Next, the correlations were analyzed between the functional status at *two months* and the same sustained attention scores as described above. For this outcome, measured at two months, 25% of the correlations were significant. Thus, the authors concluded that the total number of significant correlations with sustained attention was higher for functional outcome at two years than at two months. Moreover, a multiple regression analysis was performed, with the sustained attention measures and the two month functional status as possible predictors and with a test of contralesional hand dexterity at two years as criterion variable. The regressions showed that functional status and one of the measures of sustained attention were significant predictors of hand dexterity. According to Robertson and colleagues, these results indicate that there might be a causal relationship of attentional performance on functional outcome.

As exemplified by the studies above and the observations in this thesis, neglect and symptoms related to VSN are associated with inferior outcomes after stroke and especially so for the more complex measures of ADL. The current results are in accordance with previous literature indicating that improvement in VSN is related to decreased risk of functional dependency.

The studies presented in this dissertation also suggest that the relative importance of the lateralized symptoms of VSN, compared to processing speed, seems to diminish over time with regards to their predictive strength of functional outcome. In Study II it was found that symptoms of VSN predicted dependency at two years after stroke but that this relationship became non-significant when the processing speed measures were added. As such, it is possible that the observed predictive ability of VSN in the early phase after stroke for later functional outcome might be related to the close association between speed and VSN (see below).

Overall, the above results suggest that studies aimed at investigating recovery and functional outcome after stroke should not only differentiate between presence and absence of visual neglect, but also differentiate between the more specific symptoms of neglect, especially the nonlateralized component of visual speed.

Processing speed and functional outcome.

As reviewed above, previous studies have repeatedly shown that occurrence of VSN and visual inattention after stroke can predict an inferior long-term outcome. The studies presented in this paper suggest that a nonlateralized visual attention function (processing speed) is an important symptom of the VSN phenomenon and also an independent predictor of later outcome after stroke. In fact, based on the tests and measures utilized in the current studies, it was found that processing speed had the strongest relationship to long-term outcome of the assessed symptoms. Further support for the association between performance in processing speed at the early post-acute phase and later functional outcome can be seen in the illustration of change in score in the mRS over time (Figures 8 and 9). Overall the figures indicate that being relatively slow (medium slow and slow groups) on the Letter Cancellation test early after a stroke is associated with higher incidences of dependency at later stages and a decline in the ability to perform functional activities over time. These observations suggest an increasingly negative influence of early slow processing on functional outcome as time passes. However, it should be noted that the comparisons across follow-ups are post-hoc and mainly descriptive in nature.

As processing speed has been shown to predict long-term functional outcome (Studies II and IV) and also to be concurrently associated with outcome at three months (Study III), the relationship between speed and outcome seems to be continuous. That is, in at least some of the patients, early post-stroke impairment in processing speed may persist over time and this impairment is negatively associated with measures of later stage outcome. In the current papers the designs did not allow for investigations into the potential mechanisms underlying the observed performances in the tests of processing speed or any possible causal associations between slow processing speed and the outcome measures.

However, there is some evidence that relate abnormal changes of the cerebral white matter to speed and to activities of daily living. In a recent review article, Schmidt and colleagues (2011) found that lesions in the cerebral white matter are associated with stroke and decline in cognitive and functional abilities. Impairments in processing speed measures have often been observed in relation to various disorders which influence the white matter of the brain. Studies have shown that processing speed tends to be slowed in patients suffering from disorders such as low-grade gliomas (Ek, 2010), multiple sclerosis (Covey, Zivadinov, Shucard, & Shucard, 2011), diffuse axonal injury following traumatic brain damage (Felmingham, Baguley, & Green, 2004), early subclinical stages of vascular dementia (Almkvist, 2003), and cerebral small vessel disease (van Dijk et al., 2008; Prins et al., 2005). It has also been suggested that a stroke, possibly as an intermediate symptom of a progressive vascular disease, may be related to a steeper decline of pre-existing cognitive impairments, including impairments in processing speed (Amberla et al., 2004; Prins et al.). Some evidence indicate that the degree of white matter changes in elderly post-stroke patients predicts processing speed performance (Jokinen et al., 2005) and functional outcome at a one year follow-up (Leonards et al., 2009). Studies have also shown a relationship between changes to the white matter and processing speed in healthy samples (Kerchner et al., 2012; Madden et al., 2008; Penke et al., 2010) and general populations (Au et al., 2006; Vannorsdall, Waldstein, Kraut, Pearlson, & Schretlen, 2009; Vernooij et al., 2009) of older adults. Moreover, findings indicate that the rate of decline over time in instrumental activities of daily living in non-demented older adults is related to measures of cognitive functions, including processing speed (Dodge, Du, Saxton, & Ganguli, 2006) and that the rate of transition to disability in nondisabled elderly may be associated with age related changes in the white matter (Inzitari et al., 2009).

In the studies reported in this thesis, the possible relationships between processing speed and functional outcome with damage to the white matter was not assessed. A future extension of the current dissertation will be to investigate the associations to white matter damages which, together with further negative influence of the stroke, can have impact on long-term functional outcome and processing speed.

Measuring Processing Speed

In many of the neuropsychological tests typically used for assessing processing speed, performance tends to depend upon the capability of several cognitive and motor functions. For instance, with the Trail Making Test – A (Reitan, 1955) and Digit-Symbol coding test of the Wechsler Adult Intelligence Scale III (Wechsler, 1997), motor ability of the hand and arm, and memory can influence the observed speed of performance. Also, efficiency of visual search is an important component, especially in the Trail Making Test – A. Another test often used to measure processing speed, is the reading part of the Stroop test (Golden, 1978). In this test the results may be influenced by the participants' ability to read. As exemplified by these tests, measurements of processing speed in neuropsychological studies are seldom "pure" assessments of a mental speed factor. Similar considerations are relevant for the measures of speed used in the studies of the current thesis. As such, the designs of the current papers did not allow for specific investigations into the potential mechanisms underlying the observed performances in processing speed.

However, one may still speculate about tentative factors behind the slow performance in the present studies. In the light of previous studies of impairments associated with right hemisphere damage and neglect (Corbetta & Shulman, 2011; Husain et al., 2001; Husain & Rorden, 2003), some components seem more likely than others. An impairment of alertness or sustained attention may have resulted in a general slow performance. Also, a disorganized search for targets and/or impaired spatial working memory could potentially have led to slower speed as a result of a longer total distance of visual scanning or re-visiting of already identified targets. It might also be that some patients, for instance due to residual or mild asymmetric symptoms, spent longer time in the exploration of some part of the test sheet, resulting in slower total speed scores.

An impairment of the ability to disengage the current focus of attention (Posner et al., 1984), either toward one side of space or bilaterally (Rengachary et al., 2011), could have influenced the speed negatively as the process of reorientation of the focus could slow down the speed of visual search and target detection. It is also possible that more general psychological factors like mental fatigue (Langner, Willmes, Chatterjee, Eickhoff, & Sturm, 2010) might have influenced the results. Slowed motor-actions in the hand are a less likely component since most of the patients used their unaffected right hand.

After taking these different possibilities into consideration, it is still important to consider that the speed scores in the present studies were correlated with inferior functional outcome also after controlling for the overall neurological deficits and for the asymmetric neglect symptoms. Thus, the speed component provided information about long-term outcome over and above the classical asymmetric symptoms of neglect and the common physical neurological symptoms.

Even though conventional clinical tests of processing speed not represents “pure” measures of a speed capacity, the performance in such tests tend to be associated with diverse measures of functional outcome. The results of the current studies have lent further support for this important relationship. This thesis has also shown that impairments of processing speed, even when assessed early after stroke, can contain valuable prognostic information. Thus, regardless of the precise components behind the slowed performance, this type of measures is valuable in the clinical practice.

Pattern of Recovery from VSN

Studies I and III further confirmed previous findings that, despite marked and significant overall improvements in patients with moderate to severe post-acute VSN, recovery within the first months can be incomplete. In Study III, for the VSN and Mild symptoms group, processing speed was the symptom with the least improvement relative to the control group. Further, for the VSN group it was observed that a higher proportion of patients showed persisting symptoms of general inattention (i.e. omissions) compared to the lateralized symptoms. Partial correlations, controlling for the overall influence of omissions, identified post-acute processing speed and ipsilesional bias as the most important predictors of neglect severity at the follow-up three months after stroke. These two symptoms were also found to retain much of their effect when the scores of the separate VSN measures at *follow-up* were used in concurrent partial correlations with VSN severity at three months. The observation that improvement of VSN, across time after a right hemisphere stroke, can be incomplete has also been frequently reported in other studies (e.g., Cassidy et al., 1998; Farné et al., 2004; Hier et al., 1983; Jehkonen et al., 2007; Kettunen et al., 2012; Nijboer, Kollen, et al., 2013; Ringman et al., 2004; Wade et al., 1988). For instance, Rengachary et al. (2011) investigated differences in reaction time between the left and right visual field in patients with neglect in clinical tests two weeks after stroke. The patients were divided into two groups based on whether or not they had persisting symptoms of neglect at a 9 month follow-up. At baseline both groups had longer reaction times to stimuli presented in the left visual field compared to the right field. Overall, both groups showed marked improvements in the reaction time difference between the left and right visual field. However, for the patients who were classified as having persisting symptoms of neglect at the follow-up, visual inspection of the reaction time data show that they still had slower reaction times to targets in the left visual field.

Variability in improvements from VSN.

Results have been reported indicating that continuous improvements towards recovery are not always the case for patient with symptoms of VSN. For instance, Appelros and coworkers reported that neglect patients could show deteriorations in symptoms from one test session to the next, and Jekhonen and colleagues (2007) observed that in some patients, after an initial improvement from VSN, further recovery was discontinued as their test scores fluctuated around the cut-off for neglect for a year after stroke. In support of such previous findings, the results of Study III indicated that a few of the patients with post-acute subclinical symptoms showed some deterioration in performance from baseline to the three month follow-up.

Persistency and Interactions of Lateralized and Nonlateralized Symptoms of Slow Reactions

The observations in this thesis indicate a tendency towards more persistent impairments in the nonlateralized compared to the lateralized symptoms in the VSN patients (Study III). These results are in line with previous reports. Gerritsen and colleagues (2003) studied neglect and the speed of information processing in 42 right and 46 left hemisphere stroke patients with a mean age of 65 years (range = 39-93 years) at about 4 months after stroke (range = 72-233 days). Simple and complex reaction time tasks were administered whilst neglect was assessed with a cancellation and a line bisection task and also judged by a neuropsychologist as absent, mild or severe. Among the patients with right hemisphere stroke, the patients with neglect were significantly slower than the non-neglect patients and the patients with no neglect were significantly slower than the control group. Thus, the results suggested persisting impairment in speed in the right hemisphere patients with the most severe impairment in the patients with VSN.

Results presented by Rengachary et al. (2011) and Samuelsson et al. (1998) indicate that when patients, who have VSN relatively early after stroke are differentiated into groups of “improved” or “persisting” VSN at follow-up, the performances of the improved patients closely approach the level of controls and references. This observation seems to be true with regard to both left vs. right asymmetry and overall reaction times. The patients with persisting VSN on the other hand still perform markedly inferior compared to controls and reference patients. Furthermore, in a study by Rengachary et al. (2009) the results on a computerized task showed that patients with significant VSN at baseline had a large variability in performance at follow-up, reflecting substantial spread of the scores obtained within this group at follow-up. Although it is indicated that patients who have improved from VSN show reaction time performances that is approaching the level of controls, visual inspection of the follow-up data presented in the study by Rengachary and colleagues (2011) suggest that the reaction times of the improved group did not fully reach the level of the controls. This observation was not explained by asymmetric differences in performance between contra- and ipsilesional side and the observation thus indicates persisting mild nonlateralized impairment in reaction time.

Samuelsson and colleagues (1998) separated "recovered" from "not recovered" neglect patients (assessed at 1-4 weeks and 6-7 months after stroke). In a simple auditory reaction time task, the recovered patients showed significant improvements in performance, approaching a level close to that of controls and patients without a history of neglect. On the other hand, patients with persistent neglect showed no improvement in this task.

Taken together the literature reviewed in this thesis suggests that residual impairments of lateralized and nonlateralized visual attention may exist at later a stage after stroke, even in patients who do not show VSN in conventional tests. In the long run these persisting symptoms might be more pronounced for nonlateralized than lateralized symptoms. The sensitivity in detection of such subclinical symptoms is thus dependent upon the characteristics of the tests that are used (Jehkonen et al., 2006; Rengachary et al., 2009).

The Results in Relation to Attentional Models of VSN

A specific importance of an ipsilesional bias in the neglect phenomenon has been emphasized in several studies (e.g., Kinsbourne, 1993; Mattingley, Bradshaw, et al., 1994; Webster et al., 1995). In Studies II - IV, two measures of lateralized visual inattention (asymmetry of omissions and ipsilesional bias) were assessed. In general, Studies II and III showed that at the initial weeks post stroke both asymmetry and ipsilesional bias were fundamental components of the neglect phenomenon and both these symptoms were significantly correlated with functional outcome at three months post stroke. Actually, at the early stage, asymmetry of omissions, bias of initial orientation and overall omissions were significantly correlated to each other and to functional outcome three months after stroke. However, in the longer perspective (several years post stroke) the initial symptoms of asymmetry and ipsilesional bias were less important as predictors of outcome (Study II and IV) and at three months post stroke the presence of asymmetry and bias was evidently less salient (Study III).

Studies II - IV also assessed measures of nonlateralized visual impairments in terms of visual processing speed and overall number of omissions. Also, repetitions of previously detected targets were assessed in study II. Slowed processing speed was frequently found in the current sample and most of the patients in the functionally dependent group had symptoms of post-acute slow performance. This observation is in line with the notion that the nonlateralized intensity component of attention might be related to recovery from deficits following a right hemisphere stroke (Robertson, 1993, 2001; Robertson, Ridgeway, et al., 1997), although this tentative relationship was not investigated in this thesis. Slow processing speed was also found in some of the patients in the functionally independent group, but in these cases the symptoms were less severe.

Robertson and coworkers have shown that alleviation of nonlateralized attentional components can temporarily improve the symptoms of lateralized neglect and the level of independent performance in everyday activities (Robertson et al., 1998; Robertson et al., 1995; Wilson et al., 2000). Results like these suggest that there is an interaction between the spatially lateralized and nonlateralized symptoms, and that the combination of these symptoms may result in more severe VSN. In the current thesis it was found that initial post stroke lateralized and nonlateralized symptoms both are predictors of later VSN severity, providing further support for the importance of the interaction between these symptoms.

Non-acute Brain-damages and VSN

In Study I the influence on visual inattention by an additional non-acute brain-damage was explored. The results suggest that a possible effect of a non-acute damage can be that the patients exhibit neglect of the space ipsilateral to the acute damage (ipsilesional neglect). Ipsilesional neglect has been described previously in the literature (Kim et al., 1999; Na et al., 2000, Robertson et al., 1994) and the mechanisms behind this phenomenon have been discussed as such a pattern of performance is contradictory to the expected behaviour in neglect. Robertson and co-workers observed ipsilesional neglect in patients at a chronic stage after stroke and the authors suggested that a learned overcompensation of the initial contralesional neglect might be a reason behind ipsilesional neglect. Kim et al. and Na et al. found that ipsilesional neglect also can occur at the acute stage after a stroke. This observation suggests that overcompensation cannot be the only reason for ipsilesional neglect. Other studies have shown that ipsilesional neglect can be more frequent following LBD (Halligan, Burn, Marshall, & Wade, 1992) and in patients who exhibit mild inattention in the tests (Halligan et al; Marshall & Halligan, 1989). The observations made in Study I imply that knowledge of the history of brain-damages is important since it may explain the occurrence of unexpected inattention towards the same side as the acute brain-damage. However, the current sample was small, with only seven patients having non-acute damages contralateral to the acute damage. Furthermore, most of the studies described above did not specify the presence or absence of non-acute brain-damages. Thus, further studies are required to analyse the tentative mechanisms behind ipsilesional neglect.

An additional finding in Study I was that in 4 of the 9 patients with acute lateralized visual inattention, the effect of the non-acute damage seems to be restricted to the symptoms of visual inattention. That is, the lateralized visual inattention symptoms were ipsilesional to the acute damage, whilst the neurological symptoms were observed contralesional.

In Study III, it was observed a non-significant tendency towards a higher proportion of patients with previous brain-damages in the groups with symptoms of VSN, compared to the group with no symptoms. This pattern was not observed in Study I. A possible reason for this discrepancy might be the use of several tests and of continuous measures in Study III. This may have improved the sensitivity in detecting patients with symptoms of VSN. As such, it could be that previous damages can somewhat increase the probability of at least mild or subclinical VSN. Further analyses of the MR data will hopefully help to clarify this issue. However, regarding functional outcome, the occurrence of CT and clinically verified brain-damages prior to the index stroke were evenly distributed between the different outcome groups suggesting that previous infarcts was not an indicator of later outcome in the current study.

Strengths, Limitations and Related Discussions

Several aspects concerning limitations of the studies have been discussed in relation to their relevant sections earlier in this paper.

Tests and Measures

The conventional paper-and-pencil tests used to assess VSN in the current studies might not be sensitive enough to detect all patients with VSN, especially for mild or subclinical symptoms at the three month follow-up. Thus, the number of patients with signs of neglect identified at this follow-up might have been underestimated. However, as briefly reviewed in the introduction, the conventional paper-and-pencil tests of VSN have a good to acceptable sensitivity in detecting neglect within the acute or early post-acute phase after a stroke. Also, the use of this type of tests with a relatively low level of complexity probably led to less exclusion of patients at the early post-acute stage of the assessment and thus could strengthen the clinical relevance of the results. As a main aim was to accomplish an early assessment of possible predictors, the use of these tests was purposely chosen to be applicable in an acute stroke setting.

Several modifications of the design were made in studies II – IV in order to obtain different key symptoms of neglect early after stroke, examples of such modifications are inclusions of multiple tests, continuous data, and measure of asymmetry and ipsilesional bias. These measures were averaged scores calculated across several different tests and the results might reflect differences not controlled for in the tests graphical layout and in their variation in sensitivity to the symptom that they were supposed to measure. On the other hand, the use of multiple tests with continuous data for each measure provided the possibility for differentiated analyses of the relationships with functional outcome.

The different measures of symptoms related to VSN in this thesis were derived from the same set of test. This means that the scores in the measures were more or less correlated with each other. Such correlations might influence the results by obscuring the relative influences of the independent variables. However, in the regression analyses, tests of multicollinearity were performed and, when appropriate, offending variables were removed from the analyses. The regression analyses performed in this thesis were mainly used for assessing the relative importance of the variables and due to moderately inter-correlated variables; stepwise procedures were used in hierarchical or blocked analyses.

Assessments of functional outcome with the mRS were done by two different administrators. Researchers have found the inter-observer reliability of the mRS to be moderate (Banks & Marotta, 2007; Quinn et al., 2009). In order to meet this problem, both administrators utilized the same semi-structured interviews. Further, in cases where the administrators were in doubt they consulted with each other and with a third experienced neurologist to increase the reliability of assessment.

Study Design

Other variables than those included in this paper may represent important predictors of functional outcome. One such variable is anosognosia (unawareness of deficits). This phenomenon has been associated with VSN and poor functional outcome in previous studies (Appelros et al., 2002; Pedersen et al., 1997; Vossel, Weiss, Eschenbeck, & Fink, 2013).

Another possibly influential variable that has been linked to VSN is visuospatial short-term memory (Corbetta & Shulman, 2011). In Study II a measure that might be related to visuospatial short-term memory (Husain & Rorden, 2003; Husain et al., 2001) was included (the number of repetitions of previously identified targets). However, in the current study, this measure did not show a strong relationship with functional outcome as did the other independent variables.

It can also be that presence of depression might influence the results. However, to assess depression in the early phases after stroke is a complex task. Due to factors like the acute symptoms and the emotional turmoil often experienced by patients in the acute and post-acute phases, it is difficult to reliably differentiate depressive symptoms from other manifestations such as psychological, physical, and motivational aspects, amongst others.

Years of education and level of general cognitive impairment was only obtained and analyzed at the 7 years follow-up (Study IV). This is a limitation since these components might have influenced the outcome of the analyses in the earlier follow-ups (Studies I-III).

The use of one test only and a cut-off level for the classification of neglect in Study I probably led to a less effective identification of VSN patients. On the other hand, the use of presence or absence as the classification of VSN allowed for an inclusion of patients who were identified through a retrospective analysis of the medical records. Thus, rather than excluding patients with aphasia or severe neurological deficits the analyses were improved by minimizing the amount of missing data. To counteract the limitation by the use of one test only in Study I, the Star Cancellation test was chosen as it has been shown to be a sensitive clinical test of VSN at the early stage after stroke (Halligan et al., 1989; Lindell et al., 2007; Rengachary et al., 2009). This test is also accepted by most patients even at an early stage after stroke

A major strength of the studies presented in this dissertation was the relatively large and consecutive sample. In addition, the prospective nature of the SAHLSIS allowed for a longitudinal design in all 4 studies. As such, a large proportion of the patients who could not be included in the main analyses were still followed with regards to the reasons for why they were not included and how they scored on the background variables. As comprehensive missing-analyses were possible, a broad picture of functional outcome over time, in relation to symptoms of VSN, could be described.

In longitudinal studies different events concerning health, coping and intercurrent diseases beside late effects of the index stroke alone can influence long-term outcome measures, and new events or progressive cerebral dysfunction can also cause a decline in functioning or hampered recovery. However, it is difficult to control for all such possible variables. In the current studies patients with recurring strokes/TIAs were excluded from the longitudinal analyses. Nevertheless, despite possible negative influences of uncontrolled variables related to declining overall health, robust associations to early post-acute symptoms were observed.

Generalization

The sample did not include patients older than 69 years at the index stroke and thus, the results cannot be generalized to the total stroke population. On the other hand severe comorbidities and diffuse and multi-localized lesions are more common in an elderly stroke population. As such, by having a relatively young sample a more reliable investigation and description of the research aims were possible. In studies II-IV the sample consisted of only right hemisphere damaged patients whereas neglect can also be observed after left hemisphere damages. However, VSN after left brain damage tends to recover faster than after right hemisphere damage. Moreover, the presence of aphasia and paresis of the dominant right hand after a left hemisphere stroke can result in invalid results from the attentional and speed tests - measures that constituted main measures in these studies.

The area of interest and focus for this thesis was the long-term outcome related to the symptoms often observed after right hemisphere damages. The focus on only one main type of stroke (infarction) and on only one hemisphere (right) was adopted to improve the homogeneity of the sample in relation to the main aim.

In Study IV patients with new strokes, death or missing follow-up were not included in the analyses for functional outcome at 7 years (Table 1 in Study IV). Overall, these three groups, especially those who died, had worse scores early after stroke in several measures compared to the included patients. These differences seemed to be most pronounced in the nonlateralized measures. This observation can also be seen as an interesting result by its own. That is, the level of early post-acute impairments of visual attention and speed might be related to death within 7 years (Oksala et al., 2009). Ten patients were not included in Study IV due to missing scores on processing speed and visual attention. Six of these ten patients had scores in the outcome variables at 7 years with inferior scores in the mRS and MMSE and more severe post-acute overall stroke symptoms compared to the patients with complete data. Thus based on these observations, it is likely that the patients not included due to death or missing data have led to fewer patients with dependency and inactivity at 7 years.

In Study IV cognitive impairment, assessed by the MMSE, was included as a background variable. No significant relationship was observed between the outcome variables and MMSE. This suggests that the general cognitive level at the time for the follow-up cannot explain the obtained relationship between the post-acute score of speed and the functional outcome. However, the cognitive level of the patients not included due to death or missing data is not known, actually, it is likely that these patients would have had more inferior scores (see paragraph above).

Patients with brain damage before the index stroke were included in the studies in this thesis. The decision to include patients with previous brain damage is related to the overall goals of the dissertation. That is, the aims were to explore and describe relationships between different symptoms of VSN and functional outcome in a consecutive and clinically relevant sample rather than investigating underlying mechanisms of these relationships. Moreover, the generalizability would deteriorate by more exclusions and the presence of previous brain-injuries was assessed and included in the analyses. Therefore, possible influences of these damages could be evaluated.

Statistical Considerations

In the studies presented in this thesis the scores of the modified Rankin Scale was dichotomized into two groups. One group included all patients able to carry out all usual activities or unable to do so but able to look after own affairs without assistance (scores ≤2). The other group included all patients who required help of others at different levels (scores >2). This cut-off level makes clinical sense and is commonly used in several earlier outcome studies of stroke patients to divide between dependency and independency. However, through this dichotomization, the variation towards the ends of the scale was not accounted for in the statistical analyses thus reducing the information obtained, for example between "no symptoms" or "no significant disability despite symptoms".

A major aim of the thesis was to explore the predictive ability of different symptoms assessed at an early phase after stroke for later outcome. In stroke patients tested early after a stroke, while still in acute hospital care, the distribution of the scores tends to be heavily skewed rather than being formed like a normal curve. That is, many of the patients will exhibit severe symptoms resulting in skewed distributions towards one extreme end. Also, in some tests, a "U" like distribution can occur as some patients perform close to the "no symptom level" of the scores whereas other patients, with more severe symptoms, score close to the worst possible score. As such, robust and rather conservative analyses and outcome measures were chosen for the studies in this thesis.

Most of the analyses in this thesis are of early post-acute scores as predictors of outcome. However, in Study III, a within-group analysis was performed regarding pattern of change in VSN symptoms from the early post-acute phase to the three months follow-up. Large and highly significant improvements in scores were observed. No control group was included in the analysis and thus it was not possible to control for the effect of regression to the mean and learning effects. On the other hand, for some of the tests, it is expected that a normative sample of neurological healthy participants would show scores at, or close to, zero at both test occasions. The rationale for this is that scores on clinical measures such as tests of asymmetrical symptoms of neglect and visual field deficits are sensitive to clinical signs after a brain dysfunction but a normative sample will typically not show any or very small variation in these types of measures.

Future Research

Little is still known about the different aspects of neglect at a late stage after stroke and it is essential to conduct more investigations at several years after the stroke. At this late stage it is also important to include more sensitive tests for the different aspects of the neglect phenomenon. Further, it is essential to develop assessment methods for aspects that so far have been overlooked; one such example is the identification and quantification of an initial ipsilesional bias in the orientation of attention. After including more refined and sensitive tests, an interesting question is to what extent different key aspects of neglect still exist at a long-term follow up and to what extent such components are related to the level of activity and participation at this late stage.

In future studies assessing the influence of different VSN symptoms on later functional outcome, a separation of "recovered" patients from patients with "persistent" VSN, should be done. Such a procedure will be helpful in investigating whether subclinical symptoms of VSN patients might be clinically important. However, differentiation into several sub-groups that are related to the VSN phenomenon is challenging as such groups tend to be small and also because sensitive tests are required.

The possible mechanisms behind the robust relationship between early post-acute processing speed and long-term functional outcome represent another important subject for further exploration. It is also interesting to investigate how the component of processing speed changes across time (across many years) and the relationship between processing speed and functional outcome if both these components are tested at the time for the long-time follow-up. Another question to address is if more sensitive and differentiating measures of processing speed can provide further information regarding the association with functional outcome. In future research it is important to include tests of speed that is not dependent on visual exploration. That is, measures in which the influence of visual neglect is minimized or controlled for.

Another important issue for further research is the question about other possible confounders that can have influenced the relationship between speed and functional outcome, such as fatigue, depression and overall level of physical activity during the day. Also, by including measures of the brain damage and of the white matter of the brain, possible structural and physical components behind slowed processing could be analyzed. Our research group is currently working on investigating these questions.

In most of the studies of this dissertation only right hemisphere damaged patients were selected. Further research should also explore whether the observed relationship between later outcome and early processing speed will be present even in an unselected consecutive sample of stroke patients. This is another research objective we will explore in our research group.

Summary and Clinical Importance of the Results

The strong relationship between functional outcome and impaired processing speed might have important implications regarding the methods used when examining stroke patients. The results of Study II -IV suggest that assessing specific symptoms related to VSN using continuous data, may provide more clinically relevant information compared to only classifying VSN as present or not. It is also likely that adding measures of the localization of the start of performance will result in more sensitive assessments for the identification of neglect. The lack of standardised methods for assessing right capture of attention in orientation underlines the need for development of clinical tests of this phenomenon.

The results of our longitudinal investigations emphasize that by including only simple paper-and-pencil tests of neglect at the early post-acute stage, important prognostic information can be obtained. Furthermore, the prognostic information can be significantly improved by adding some specific registrations. Hereby information can be gained that can assist in planning of the potential need of rehabilitation or assistance in the future. The first such important registration is of an initial orientation of attention toward the same side as the brain damage (ipsilesional) and omissions of important information toward the contralesional side. The presence of this behavior indicates that the patient will have an elevated risk of experience extra difficulties in attaining independency in daily activities in the future. These signs are important to register at the early post-acute stage since they often are difficult to detect at a later stage due to the recovery from these symptoms. The relationship with poor functional outcome may however remain.

Secondly, by including timekeeping to a visual cancellation test even more important prognostic information can be obtained regarding the possibility of difficulties in attaining independency many years after the stroke event. For example, in the present thesis it was found that a cut-of level of 2,3 seconds per cancelled target in a letter cancellation task at the post-acute stage, effectively differentiated between inactive patients in instrumental daily activities and those with a high activity level seven years post-stroke.

Due to the patients included, these findings are restricted to patients with a right hemisphere stroke and to patients below 70 years at the stroke event. The presented papers indicate that a slow visual processing speed is an important component to focus upon in the early prediction of long-term functional outcome. However, this thesis did not investigate which measure that may be the optimal choice and further research is needed for identification of the optimal tests and cut-of levels for clinical use at the early post-acute stage.

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