Visuospatial inattention and processing speed: Predictors of long-term outcome and patterns of change after ischemic stroke

Joel Gerafi

Doctoral dissertation in Psychology
Department of Psychology
University of Gothenburg
November 29, 2019

Printing: BrandFactory AB, Kållered, Sweden, 2019
ISBN: 978-91-7833-713-2 (Print)
ISBN: 978-91-7833-712-5 (PDF)
ISSN: 1101-718X Avhandling/Göteborgs universitet, Psykologiska inst.
Web: http://hdl.handle.net/2077/62154

DOCTORAL DISSERTATION IN PSYCHOLOGY

Gerafi, J. (2019). *Visuospatial inattention and processing speed: Predictors of long-term outcome and patterns of change after ischemic stroke.* Department of Psychology and the Stroke Research Group at the Department of Neuroscience and Physiology, the Sahlgrenska Academy, University of Gothenburg, Sweden.

ABSTRACT

Impairments of visuospatial attention, language, and processing speed (PS) are common early after stroke and have been associated with unfavorable short-term functional outcomes but little is known about this relationship in the long-term. This thesis investigates 1) the potential importance of visuospatial inattention (VSI) and language impairments (LI) as predictors of functional outcomes 7 years after an ischemic stroke (studies I-II) and 2) presence of lateralized inattention 7 years after stroke and potential predictors of this phenomenon (study III). Study IV gives a detailed description of the long-term course of PS across 3 months and 7 years after an ischemic stroke. A cohort of 375 consecutive stroke patients was assessed early after stroke for the occurrence (studies I–II and IV) and severity (studies III-IV) of VSI using the Star Cancellation Test (SCT, studies I-IV) and Letter Cancellation Test (LCT, studies III-IV). Language impairments were investigated (studies I-II) by the language item from the Scandinavian Stroke Scale (SSS). At the 7-year follow-up, functional outcomes were measured by the modified Rankin Scale (mRS), the Frenchay Activities Index (FAI) (studies I-II and IV), and the recovery item of Stroke Impact Scale (SIS) (study IV). Patients with a recurrent stroke during the follow-up period were excluded (all studies). The presence of lateralized inattention at the 7-year follow-up (study III) was assessed with the SCT, the LCT, and the neglect item from the NIH Stroke Scale (NIHSS). The long-term course of PS (study IV) was measured by a mirrored copy of the SCT with a time limit of 30 seconds, follow-up assessments of SCT, LCT, and NIHSS were also included in this study. In **study I**, 235 stroke survivors were included at the follow-up and VSI and stroke severity (SSS) were identified as the significant independent predictors of unfavorable outcomes in mRS and FAI. The early screening of LI did not provide independent prognostic information beyond the information provided by VSI and stroke severity. In **study II**, 105 individuals with left hemispheric stroke were included at the 7-year follow-up. It was found that the presence of VSI was rather common observed in about one of five patients. VSI was the most important independent predictor of unfavorable outcomes in mRS and FAI. Individuals with both VSI and LI had increased risk of poor outcome compared to those with signs of one of these symptoms. In **study III,** 188 stroke survivors were included at the 7-year follow-up and about one of ten had signs of lateralized inattention. Independent baseline predictors for these long-term signs were total omissions in target cancellations and inferior performance on visual processing speed. In **study IV,** 148 subjects were included at follow-up and impaired PS was observed in about one of three individuals at baseline with significant improvement in scores at 3 months followed by a clear decline at 7 years. It was also found that slow PS was related with inferior functional outcome at the 7-year follow-up, also after adjusting for age. Age was related with scores in PS but did not explain the scores of PS for those with lowest speed.

Conclusions: Studies I-II emphasize the importance of identifying early symptoms of VSI not only after right hemispheric stroke but also after left hemispheric stroke and particularly for individuals with severe symptoms of LI. A combination of attention and language deficits at the acute phase seems to be rather common among patients with left hemispheric stroke and indicates an increased risk of unfavorable outcomes. Studies III-IV are the first studies to recognize PS as a significant predictor of long-term lateralized inattention and to describe changes in speed across two follow-ups up to 7 years in a stroke cohort. The results from these two studies emphasize the importance of further long-term studies of PS after stroke.

Keywords: visuospatial inattention, language impairment, long-term functional outcome, ischemic stroke, neglect, aphasia, lateralized inattention, processing speed

Joel Gerafi, Department of Psychology, University of Gothenburg, P. O. Box 500, 405 30 Gothenburg, Sweden.
E-mail: joel.gerafi@psy.gu.se

SWEDISH SUMMARY
(Svensk sammanfattning)

Stroke (slaganfall) är ett samlingsnamn för hjärninfarkt och hjärnblödning och är en av våra stora folksjukdomar som drabbar ca 30 000 svenskar årligen. En hjärninfarkt (ischemisk stroke) är den vanligaste typen av stroke där en blodpropp i hjärnan orsakar syrebrist som utan snabb behandling leder till celldöd. Hjärnblödning (hemorrhagisk stroke) är mindre vanlig och karaktäriseras av att syrebrist uppstår i det drabbade området till följd av att blodkärl brister. Ett insjuknande i stroke innebär ofta avsevärda hinder i den drabbades liv.

I det tidiga (akuta) skedet efter en stroke är nedsatt rumslig uppmärksamhet (spatial neglekt) och nedsatt språkfunktion (afasi) vanliga symptom. Neglekt förekommer oftast efter stroke i höger hjärnhalva och afasi vid stroke i vänster hjärnhalva. Dessa symptom kan medföra stora hinder i den drabbades liv då neglekt innebär omedvetenhet om objekt och företeelser på motsatt sida av hjärnskadan. Vid en högersidig stroke missar därför individer viktig information på vänster sida, exempelvis text när de läser, bestick när de äter och personer som finns till vänster i rummet. En annan konsekvens är att det blir svårt att hitta i den närmaste omgivningen. Symptomen vid neglekt kan påverka individen på alla plan i livet, från basala vardagliga sysslor till deltagande i samhället i stort och i arbetslivet. Afasi innebär nedsatt förmåga att kommunicera verbalt med andra människor och budskap kan feltolkas eller missförstås. Förmågan att uttrycka sig i skrift kan också vara nedsatt. Detta påverkar förmågan till delaktighet i samhällsaktiviteter, fritid och arbetsliv.

I det korta perspektivet, inom ett år efter strokeinsjuknandet har neglekt och afasi studerats ingående och ett klart samband har påvisats mellan minskad självständighet i vardagen och förekomsten av dessa symptom. I nuläget saknas studier som beskriver hur detta samband ser ut på längre sikt, flera år efter insjuknandet. Denna brist på kunskap visar på ett angeläget forskningsområde. De flesta individer med neglekt visar en god återhämtning, speciellt under de första tre månaderna. I nuläget saknas det kunskap om hur återhämtning av neglekt ser ut på längre sikt, efter det första året efter stroke, samt vilka faktorer efter insjuknandet som har ett samband med kvarstående neglekt.

En vanlig kognitiv nedsättning efter stroke är en nedsatt visuell bearbetninghastighet. Ett klart samband har påvisats mellan en försämrad hastighet, nedsatt förmåga i dagliga sysslor och förekomst av nedsatt uppmärksamhet men det finns väldigt få studier som har undersökt hur förändringar av bearbetninghastighet ser ut över tid, speciellt i det längre perspektivet, flera år efter ett strokeinsjuknande. Det saknas också kunskap på längre sikt om hur sambandet ser ut mellan dessa förändringar och förekomst av nedsättningar av visuell ouppmärksamhet och förmågan att delta i vardagliga aktiviteter.

I denna avhandling ingår fyra studier som omfattar en kohort av 375 deltagare mellan åldrarna 18 och 69 år som drabbats av en ischemisk stroke och blivit inskrivna på en akut strokeenhet. Deltagarna bedömdes i det tidiga skedet efter strokeinsjuknandet med ett enklare screeningförfarande för förekomst av neglekt och afasi. Bearbetningshastighet i en enkel avsökningsuppgift och olika neurologiska symptom registrerades också. Vid en uppföljning 7 år senare, utfördes en bedömning av funktionellt utfall i form av grad av

hjälpbehov och aktivitetsnivå i olika dagliga aktiviteter. Vid denna uppföljning fick deltagarna också göra en egen bedömning av grad av återhämtning sedan insjuknandet. Individer som drabbats av en ny stroke under dessa 7 år exkluderades.

I **studie I** inkluderades 235 deltagare som undersöktes både i det akuta skedet och vid 7 år. Syftet var att undersöka om ett enkelt screeningförfarande av neglekt och afasi tidigt efter stroke kunde ge prognostisk information om funktionellt utfall vid 7 år. Studien visade att individer med förekomst av neglekt och ökad grad av neurologiska symtom tidigt efter stroke hade ökat hjälpbehov och lägre aktivitetsnivå i dagliga aktiviteter vid 7 år. Tidiga afasisymptom tillförde inte någon ytterligare viktig information angående de två utfallen.

I **studie II** inkluderades enbart patienter med vänstersidig hjärnskada, totalt 105 individer. Syftet med studien var att undersöka till vilken grad neglekt tidigt efter stroke kan bidra med prognostisk information om funktionellt utfall vid 7 år efter en skada i den vänstra hjärnhalvan. De viktigaste resultaten från denna studie var att neglekt var ganska vanligt förekommande och hade ett högt samband med graden av hjälpbehov och aktivitet vid 7 år. En grupp av individer med symptom av både neglekt och afasi identifierades som hade ett märkbart försämrat utfall vid uppföljningen. Svåra symptom av afasi var vanligt förekommande i denna grupp och vid en utförlig ytterligare undersökning upptäcktes att svåra symptom av neglekt också förelåg. Utan denna typ av undersökning av individer med svår afasi till följd av vänstersidig hjärnskada hade inte denna grupp med svåra symptom av neglekt i kombination med afasi kunnat identifieras.

I **studie III** inkluderas 188 deltagare vid uppföljningen 7 år efter stroke. Studiens syfte var att undersöka förekomsten och prediktorer för lateraliserad ouppmärksamhet sent efter stroke, 7 år efter insjuknandet. Resultaten visade att ungefär en av tio individer hade förekomst av ouppmärksamhet vid uppföljningen. Ett ökat antal missar i screeningförfarandet för neglekt och en lägre prestation i bearbetningshastighet tidigt efter stroke predicerade förekomst av lateraliserad ouppmärksamhet vid 7 år.

I **studie IV** inkluderades totalt 148 individer vid 7 år. Syftet med studien var att beskriva förändringsmönster i bearbetningshastighet mellan det akuta skedet, vid 3 månader och vid 7 år. Studien undersökte också sambandet mellan förändringar i bearbetningshastighet över tid och funktionellt utfall, ålder, neurologisk status och visuell ouppmärksamhet. Studien visade att ungefär en tredjedel av individerna hade en låg bearbetningshastighet i det akuta skedet men att de flesta presterade bättre vid 3 månader följt av en klar försämring vid 7 år. Detta mönster skiljde sig tydligt från återhämtningsmönstret för visuell ouppmärksamhet som förbättrades kontinuerligt till 3 månader och sedan vidare till 7 år. Graden av neurologiska symtom förbättrades också till 3 månader och låg sedan kvar på denna nivå vid 7 år. Resultaten visade också att försämrad bearbetningshastighet var relaterat till ett försämrat funktionellt utfall vid 7 år, även när man kontrollerade för en ökad ålder. Ålder var relaterat till bearbetningshastighet men förklarade inte prestationen hos individer med lägst processhastighet.

Sammanfattningsvis är neglekt och afasi vanligt tidigt efter stroke. De flesta studier av samband mellan minskad självständighet i vardagen och förekomst av dessa symptom har utförts inom 3-6 månader efter insjuknandet. Studie I och II i denna avhandling undersökte detta samband 7 år efter insjuknandet i stroke. Resultaten visade fördelen med att använda ett enkelt screeningförfarande för att identifiera förekomsten av neglekt och afasi tidigt efter stroke. Med en enkel screening och en genomgång av personens journal i de fall den drabbade inte kunde medverka vid undersökningen kunde fler personer med neglekt identifieras i det tidiga skedet och detta var tydligast för patienter med svår afasi efter en vänstersidig hjärnskada. Genom att identifiera förekomst av neglekt på detta sätt framkom ett samband mellan tidig förekomst av neglekt och nedsatt förmåga i dagliga aktiviteter 7 år efter insjuknandet. Man fick på detta sätt fram viktig prognostisk information inte bara för personer med högersidig hjärnskada utan också för dem med vänstersidig skada och då framför allt de med svår afasi. En förekomst av både neglekt och afasi i det akuta skedet indikerar en särskilt hög risk för sämre långtidsprognos. Studie III är den första studien som visar att bearbetningshastighet tidigt efter stroke predicerar förekomsten av lateraliserad ouppmärksamhet 7 år efter stroke. Studie IV är också unik genom att den beskriver förändringsmönster av bearbetningshastighet vid olika mätpunkter över en 7 års period och relationen mellan dessa förändringar och funktionellt utfall.

Vidare studier med uppföljningar flera år efter ett strokeinsjuknande är viktiga eftersom de kan öka kunskapen om hur konsekvenserna efter en stroke ser ut på lång sikt. Informationen om prognosen på lång sikt är speciellt viktig, inte bara för den drabbade individen och dess anhöriga, utan även för hur planeringen av framtida stödinsatser och rehabilitering kan se ut.

PREFACE

This thesis is based on the following studies referred to by their Roman numerals.

I. Gerafi, J., Samuelsson, H., Viken, J. I., Blomgren, C., Claesson, L., Kallio, S., Jern, C., Blomstrand, C., & Jood, K. (2017). Neglect and aphasia in the acute phase as predictors of functional outcome 7 years after ischemic stroke. *European Journal of Neurology, 24,* 1407-1415. doi:10.1111/ene.13406

II. Gerafi, J., Samuelsson, H., Viken, J. I., Blomgren, C., Claesson, L., Kallio, S., Jern, C., Blomstrand, C., & Jood, K. Visuospatial inattention following a left hemispheric stroke predicts long-term functional outcome. *Manuscript unpublished.*

III. Gerafi, J., Samuelsson, H., Viken, J. I., Jern, C., Blomstrand, C., & Jood, K. (2019). The presence and prediction of lateralized inattention 7 years post-stroke. *Acta Neurologica Scandinavica. Manuscript accepted pending minor revision.*

IV. Gerafi, J., Samuelsson, H., Viken, J. I., Jern, C., Blomstrand, C., & Jood, K. Patterns of change in visual processing speed after ischemic stroke: A long-term descriptive study. *Manuscript unpublished.*

ACKNOWLEDGEMENTS

Firstly, I would like to express my sincere gratitude to my supervisor and co-author Hans Samuelsson for his dedication and guidance throughout these years, and for his valuable ideas and support. Thank you for always believing in me, I am truly grateful.

I would also like to express my thankfulness to my co-supervisors and co-authors Christian Blomstrand and Katarina Jood for their commitment in giving me the opportunity to conduct research, for sharing their deep knowledge of science and clinical practice, and for all their support and valuable feedback on all manuscripts in this thesis.

I want to thank my co-supervisor and co-author Sakari Kallio, my former teacher at the University of Skövde, for his positive attitude and for providing me with opportunities to become a doctoral candidate and to teach in various courses.

Thanks to Christina Jern for all feedback regarding my manuscripts and for sharing her broad knowledge of science and clinical expertise in the research field and in our project.

I would also like to thank my former colleague Jo I Viken for his valuable ideas and for our interesting discussions about science in general, which have been much appreciated.

I also wish to thank my co-authors Lisbeth Claesson and Charlotte Blomgren for their knowledge and feedback regarding the Frenchay Activities Index, and the SAHLSIS research-nurse Ingrid Eriksson for her assistance with data collection and the study participants.

I want to thank Björn Landström and Anneli Darheden at the Skaraborg Institute for Research and Development for engaging in collaborations during my doctoral studies and for their genuine interest and positive attitude to the SALHSIS research project.

Thanks to Jesper Lundgren, head of Department of Psychology, University of Gothenburg for his commitment in finding different solutions and collaborations during my doctoral studies and for his helpful approach.

I would also like to thank all members of The Stroke Research group and the SAHLSIS project. I feel privileged to work alongside all of you in this fascinating research area!

Last but not least, I want to thank my family and my beautiful wife Naemi for all your love, support, and patience throughout these years.

This thesis was made possible through collaboration with the Institute of Neuroscience and Physiology, the Sahlgrenska Academy at University of Gothenburg, and the University of Skövde.

LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
BI	Barthel Index
BIT	Behavioral Inattention Test
CT	Computed tomography
FAI	Frenchay Activities Index
IADL	Instrumental Activities of Daily Living
LACI	Lacunar infarcts
LCT	Letter Cancellation Test
LI	Language impairment
LVI	Lateralized visual inattention
MLI	Mild language impairment
MRI	Magnetic resonance imaging
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NLVI	Non-lateralized visual inattention
No LI	No language impairment
No VI	No visual inattention
OCSP	Oxfordshire Community Stroke Project classification criteria
PACI	Partial anterior circulation infarcts
POCI	Posterior circulation infarcts
PS	Processing speed
SAHLSIS	the Sahlgrenska Academy Study on Ischemic Stroke
SCT	Star Cancellation Test
SIS	Stroke Impact Scale
SLI	Severe language impairment
SSS	Scandinavian Stroke Scale
TACI	Total anterior circulation infarcts
VFD	Visual field deficit
VSI	Visuospatial inattention

TABLE OF CONTENTS

INTRODUCTION

Stroke is a global burden and a devastating neurological disease often causing cognitive and physical impairments, disabilities, and death. In 2010, it was estimated that nearly 17 million people worldwide suffered from a first-ever stroke and it was also reported that about 6 million were stroke-related deaths (Feigin et al., 2010). The different types of stroke are ischemic stroke (blockage of a blood vessel that supplies the brain tissue), hemorrhagic stroke and subarachnoid hemorrhage (ruptures of these blood vessels). The most common type is the ischemic stroke and the present studies focused on individuals with this type of stroke.

Lateralized disruptions of visuospatial attention is a key sign of neglect and impaired language is a key sign of aphasia and these signs are often observed at the early stage after ischemic stroke (Appelros, Karlsson, Seiger, & Nydevik, 2002; Dickey et al., 2010; Engelter et al., 2006; Pedersen, Jorgensen, Nakayama, Raaschou, & Olsen, 1995, 1997; Ringman, Saver, Woolson, Clarke, & Adams, 2004) and have been related with unfavorable short-term functional outcomes within the first year after stroke (Ali et al., 2013; Dalemans, De Witte, Beurskens, Van den Heuvel, & Wade, 2010; Gialanella, 2011; Gialanella et al., 2011; Jehkonen, Laihosalo, & Kettunen, 2006, Nesi, Lucente, Nencini, Fancellu, & Inzitari, 2014; Pedersen, Jorgensen, Nakayama, Raaschou, & Olsen, 1996; Stein, Kilbride, & Reynolds, 2016; Wade, Hewer, David, & Enderby, 1986). However, there is an obvious lack of long-term studies exceeding one year after the baseline assessment. Individuals with early signs of neglect after stroke often show improvements of these symptoms during the first three months after stroke (Cassidy, Lewis, & Gray, 1998; Nijboer, Kollen, & Kwakkel, 2013) but knowledge about the time course and potential predictors for presence of this phenomenon beyond the first year after stroke is scarce.

A common cognitive deficit after stroke is decreased visual processing speed (Barker-Collo, Feigin, Parag, Lawes, & Senior, 2010). It has been suggested that slow processing speed underlies decline in other cognitive domains such as visuospatial attention and that it correlates with presence of visuospatial inattention (Nurmi et al., 2018; Su et al., 2015; Winkens, van Heugten, Fasotti, Duits, & Wade, 2006). Impaired processing speed has also been correlated with poor long-term functional outcome (Barker-Collo et al., 2010; Viken, Jood, Jern, Blomstrand, & Samuelsson, 2014). Nevertheless, there are few studies that have examined the temporal changes in processing speed in the long-term after stroke and possible associations with cognitive impairments and functional outcome.

The main aims of the current thesis were to investigate if a basic screening of signs of neglect and aphasia early after stroke could provide prognostic information about long-term functional outcomes at 7 years post-stroke, to investigate presence and predictors for lateralized inattention 7 years after stroke, and to describe patterns of change in processing speed across this time period.

The following sections provide background information about frequency and recovery rates of neglect and aphasia, different subtypes of neglect and aphasia, as well as literature about these phenomena as predictors of short- and long-term functional outcomes. Background information and definitions of some key terms of inattention and processing speed after stroke are also provided before presenting the aims of the four papers included in this thesis. This is followed by a summary of methodology, results, and discussion. Finally, a more general discussion, ethical considerations, limitations, and concluding remarks are provided along with suggestions of further research.

Neglect and aphasia

Neglect after a stroke is typically described as the inability to orient towards and detect stimuli in the hemi-space opposite to the side of the hemispheric lesion (contralesional), even when primary sensory or motor functions remain intact (Halligan & Marshall, 1993, 1998; Tsirlin, Dupierrix, Chokron, Coquillart, & Ohlmann, 2009). The term neglect is often used interchangeably with other terms of similar meaning. This is due to the different types of neglect that exist e.g. unilateral neglect, hemineglect, hemi-inattention, hemispatial neglect, visual neglect, and visual inattention (Bowen, McKenna, & Tallis, 1999; Ting et al., 2011).

Neglect symptoms following right hemisphere stroke are reported as more common and severe compared to neglect after left hemisphere stroke (Bowen et al., 1999; Fullerton, McSherry, & Stout, 1986; Heilman, Watson, & Valenstein, 1993; Ringman et al., 2004). These symptoms are most often observed in the visual/visuospatial modality but can appear in auditory or motor modalities, or even in combination (Ogden, 1987).

Aphasia is a broader term of a cluster of impairments that affects the production or comprehension of language, and the ability to read or write. It has been described as a defect in the two-way translation mechanism between thought and language processes which can compromise language formulation, comprehension, or both (Damasio & Damasio, 2000). Symptoms of aphasia are observed after stroke in brain areas responsible for language processing, most often located in the left hemisphere (Dickey et al., 2010; Engelter et al., 2006; Pedersen et al., 1995).

Frequency of neglect and aphasia

Neglect is often caused by stroke (Corbetta & Shulman, 2011) but has been observed following other diseases as well such as Huntington's disease (Ho et al., 2003) and Alzheimer's disease (Ishiai et al., 2000). Two large studies of stroke have reported a frequency rate between 20-23% of neglect at the acute phase (Appelros et al., 2002; Pedersen et al., 1997). The frequency after right hemisphere stroke has been estimated to 43-48% by Buxbaum et al. (2004) and Ringman et al. (2004), while others reported frequency rates between 13-82% (Stone et al., 1991; Stone, Halligan, & Greenwood, 1993; Sunderland, Wade, & Hewer, 1987). This wide spread of frequency rates could be explained by large differences in subject selections, the timing of assessment after onset of stroke, the choice of assessment tools, lesion location (Bowen et al., 1999), and increased age in patients (Ringman et al., 2004).

Aphasia is often caused by acute stroke in language related areas in the left hemisphere. Other brain injuries such as tumors, head trauma, or degenerative diseases such as Alzheimer's disease can also cause aphasia given that language responsible areas are affected (Damasio & Damasio, 2000). Various studies have suggested that aphasia occurs in 30-38% of acute stroke patients (Dickey et al., 2010; Engelter et al., 2006; Pedersen et al., 1995) while lower frequency rates (21-28%) have been reported elsewhere (Brust, Shafer, Richter, & Bruun, 1976; Laska, Hellblom, Murray, Kahan, & Von Arbin 2001; Wade et al., 1986). These differences could be explained by the choice of study designs and diagnostic criteria as well as variations in sample sizes between studies (Engelter et al., 2006; Dickey et al., 2010). For aphasia a prevalence of 19% to 32% has been described for follow-up studies within 1 year with a decrease of the prevalence of 2% to 12% compared to the baseline assessment (Flowers et al., 2016).

Recovery of neglect

Most studies on recovery of neglect have differences in study settings. This is important to consider when describing the literature (Ferro, Mariano, & Madureira, 1999). For example, some studies comprise selected samples from acute hospital (Cassidy et al., 1998; Colombo, De Renzi, Gentilini, 1982) or rehabilitation center series (Levine, Warach, Benowitz, & Calvanio, 1986), while others include samples from an unselected stroke registry (Sunderland et al., 1987). Since neglect is a heterogeneous disorder and known to be a dynamic phenomenon (Ferro et al., 1999), it can be misleading to compare prevalence and recovery rates of neglect between studies, unless the definition, methods, and study settings are clearly described.

Generally, the natural history of recovery from neglect across time is that many patients improve during the first three months after the stroke and that the improvement then levels off successively up to a year after stroke (Cassidy et al., 1998; Farne et al., 2004; Jehkonen, Laihosalo, Koivisto, Dastidar, & Ahonen, 2007; Rengachary, He, Shulman, & Corbetta, 2011; Ringman et al., 2004; Nijboer et al., 2013). It has been reported that about one third of patients with neglect in the first weeks after stroke show persisting symptoms of neglect at three months or more post-stroke (Cassidy et al., 1998; Karnath, Rennig, Johannsen, & Rorden, 2011; Samuelsson, Hjelmquist, Jensen, Ekholm, & Blomstrand, 1998). During the first year after stroke, several factors have been suggested as significantly affecting the persistence of neglect, such as patients' age (Ringman et al., 2004), initial neglect severity (Rengachary et al., 2011), presence of visual field deficits (Cassidy, Bruce, Lewis, & Gray, 1999), lesion location and size (Farne et al., 2004; Hier, Mondlock, & Caplan, 1983), and brain atrophy (Levine et al., 1986). Less is known about predictors of neglect in a longer perspective.

Patterns of recovery from neglect

Although a spontaneous recovery can occur during the first months after stroke (Farne et al., 2004; Wade, Wood, & Hewer, 1988) the recovery can be both complete and incomplete (Farne et al., 2004; Hier et al., 1983; Jehkonen et al., 2007; Kettunen, Nurmi, Dastidar, & Jehkonen, 2012; Ringman et al., 2004; Rengachary et al., 2011; Wade et al., 1988). For instance, Cassidy et al. (1998) used the behavioural inattention test (BIT) to assess neglect in 66 right hemispheric stroke patients <seven days post-stroke and at monthly intervals for three months. In order to determine the recovery of neglect, the test sheet was divided into columns to the right or left of body center. The authors found a progressive improvement in BIT scores during three months for the 27 patients who had neglect on admission. A recovery was observed in both hemi-spaces but omissions were still present, especially in the left hemi-space, suggesting persisting signs of neglect. Further studies (Jehkonen et al., 2007; Levy Blizzard, Halligan, & Stone, 1995; Small & Ellis, 1994) have reported that the spontaneous recovery of neglect can fluctuate across time. In the study by Jehkonen and colleagues (2007), 56 consecutive patients with acute right hemispheric stroke were included of which 21 had visual neglect as assessed by the conventional subtest of the BIT at a 10-day examination. During the follow-ups, the authors identified a fluctuating recovery group of neglect patients ($n = 4$). At the three-month follow-up, all those patients had BIT scores above cut-off indicating a recovery from neglect. However, at the six-month follow-up all patients had visual neglect and at the one-year follow-up 2 patients still showed signs of visual neglect. Thus, these results show that for some patients an unstable neglect recovery occurs up to one year post-stroke.

Recovery of neglect in the long-term perspective

The reported numbers for patients with chronic neglect in the longer perspective vary a lot, some studies have described a neglect frequency of 10% to 15% a year or more post-stroke (Kotila, Niemi, & Laaksonen, 1986; Linden, Samuelsson, Skoog, & Blomstrand, 2005; Patel, Coshall, Rudd, & Wolfe, 2003). However, the recovery may be incomplete (Jehkonen et al., 2007; Rengachary et al., 2011) and more subtle symptoms have been observed with more demanding tasks (Bonato 2015; Rengachary, d'Avossa, Sapir, Shulman, & Corbetta, 2009).

Six follow-up studies of presence of neglect have been conducted after the first year post-stroke. Four of these were selected subgroups of right hemispheric stroke patients who had signs of neglect at the early baseline assessment: n=14 (Cherney & Halper, 2001); n=17 (Hjaltason, Tegnér, Tham, Levander, & Ericson, 1996); n=24 (Karnath et al., 2011); n=27 (Lunven et al., 2015). For three of these studies the follow-up time was at mean 1.3 years (Karnath et al., 2011), >18 months (Cherney & Halper, 2011), and >1 year (Lunven et al., 2015) and the recovery rate for baseline neglect was 67 % (Karnath et al., 2011), 43 % (Cherney & Halper, 2011), and 37 % (Lunven et al., 2015). The fourth study (Hjaltason et al., 1996) consisted of stroke patients with neglect who had been admitted at a hospital 1-5 years before the start of the study. They examined presence of neglect with different conventional neglect tests and found that 14 of the 17 included subjects showed signs of neglect in one or more of the six neglect tests. Baseline predictors of persisting neglect were investigated in the study by Karnath et al. (2011) and significant predictors were presence of a visual field deficit and higher initial neglect severity, although one of the studies reported no association with initial neglect severity (Cherney & Halper, 2001).

We identified one study (Linden et al., 2005) that comprised an unselected consecutive series of patients with a follow-up >1 year. In this study 138 old stroke patients (>70 years at index stroke) were investigated at a 20-month follow-up with the Star Cancellation Test, 15 % had visuospatial inattention and 9 % had lateralized inattention. A study by Kotila et al. (1986) investigated the prognosis of 52 surviving patients from an unselected stroke registry. The participants were examined with neurological and neuropsychological examinations after stroke onset and at a 4-year follow-up. After stroke onset 12 patients had visuospatial inattention of which seven had clear-cut contralateral neglect and five a milder form of lateralized inattention. At the follow-up, contralateral neglect was persistent in all seven subjects, and only one had recovered from visuospatial inattention. These long-term follow-ups, except two (Kotila et al., 1986; Linden et al., 2005) comprised rather small selections of right hemispheric stroke patients and complementary long-term follow-ups of unselected stroke cohorts are warranted in order to describe presence of lateralized inattention.

Neglect and aphasia subtypes

There are different subtypes of neglect with different classifications (Ting et al., 2011). These subtypes can be divided into four main categories concerning; modality (input/output), type of spatial representation, range of space (Vallar, 1998), and a category concerning representational or perceptual processing of visual information (Guariglia & Pizzamiglio, 2007; Ortique et al., 2003; Pizzamiglio, Guariglia, Nico, & Padovani, 1993).

The input modality concerns sensory neglect and is associated with the perceptual unawareness (often visual/visuospatial) of sensory stimuli in the contralesional hemi-space. The output modality concerns premotor neglect (inability to orientate the limbs towards the contralesional hemi-space), although awareness of stimuli can remain intact (Vallar, 1998).

Spatial representation (frame of reference) includes two different subtypes of neglect; egocentric and allocentric. The former is marked by a failure to spatially focus attention towards the contralesional hemi-space relative to the midline of the body (body/viewer-centered) while the latter is a failure to focus attention towards the contralesional side of the stimuli or object, regardless of the stimuli position in relation to the midline of the body (stimulus/object-centered; Adair & Barrett, 2008; Corbetta & Shulman, 2011; Vallar, 1998).

The range of space includes neglect of the individual's own body (personal), the space within the arm reach (peripersonal), and outside the arm reach (extrapersonal; Vallar, 1998).

The final category concerns representational vs. perceptual neglect (Guariglia & Pizzamiglio, 2007; Ortique et al., 2003; Pizzamiglio et al., 1993). Individuals with representational neglect are unable to visualize and describe the contralesional hemi-space of their inner mental representations. In contrast, individuals with perceptual neglect can visualize and describe their inner representations but cannot describe the contralesional hemi-space from the on-line visual perception. The difference concerns the ability to navigate and create a cognitive map of an environment by forming a mental representation based on memory recall (Pizzamiglio et al., 1993).

The current studies in this thesis did not aim to identify the different subtypes of neglect. Instead, the combination of two core components of the neglect phenomenon was registered; visual inattention (i.e. omission of visual stimulus) in combination with lateralized visual inattention (i.e. an asymmetry in such omissions).

There are also several subtypes of aphasia related to the location and severity of the brain injury (Lezak, Howieson, Bigler, & Tranel, 2012). With developments of behavioral and neuroanatomical techniques it is possible to categorize common types of aphasic syndromes by using traditional clinical classifications schemes (e.g., Table 2-2 in Benson, 1993; Table 5-1 in Damasio & Damasio, 2000). These schemes classify aphasia based on patterns of impairment and ability-sparing in verbal communication, such as speech fluency, comprehension, repetition, and naming. Four of the most common aphasic syndromes mentioned in different clinical classification schemes are; Broca's aphasia, Wernicke's aphasia, global aphasia, and conduction aphasia (Lezak et al., 2012).

Broca's aphasia is broadly accepted as the first specific type of aphasia and characterized by a non-fluent verbal output, poor ability of repetition and naming, but with fairly preserved comprehension. Individuals with Wernicke's aphasia have a fluent verbal output but with disturbed comprehension, repetition, and naming ability. Conduction aphasia features a fluent verbal output but differs from Wernicke's aphasia because comprehension is much better than repetition while naming ability remains poor. In global aphasia, all aspects of language are disturbed i.e. a non-fluent verbal output, comprehension, repetition, and naming. For further reading about clinical aphasic subtypes see Benson (1993).

The identification of language impairment in studies I-II in this thesis did not differentiate between subtypes of aphasia. Instead it was directed towards the general presence of aphasic signs in the individuals' verbal speech and communication at the acute phase.

The importance of neglect and aphasia as predictors of functional outcome

This section will give an overview of research about the possible importance of neglect and aphasia as predictors of functional outcome and it will be divided into short-term and long-term studies. Short-term studies will be defined as the time up to 1 year after the stroke, although most of the short-term studies in this overview were conducted within the first 3 to 6 months, and long-term studies will be defined as 1 year or longer. The overview will focus on functional outcome in terms of activities of daily living (ADL), both at basic and instrumental levels. Basic activities include for example our ability to manage personal hygiene, dressing, using lavatory, and moving around within the house. Examples of rating scales that include components of basic ADL and level of dependency in ADL are the Barthel Index (BI), the modified Rankin Scale (mRS), and the motor subscale of the Functional Independence Measure (FIM). Instrumental daily activities include our ability to manage for example cleaning and maintaining the house, preparing meals, moving around within the community, managing money, and shopping various necessities. Examples of rating scales that include components of instrumental activities are the Frenchay Activities Index (FAI) and the cognitive subscale of the Functional Independence Measure (FIM). FAI includes items of complex instrumental activities such as social activities, leisure activities, and work.

The overview will focus on studies of long-term functional outcome, covering most (or at best all) of these studies. The initial chapter about short-term outcome does not aim at covering all studies conducted, but serves as an illustrative example of studies conducted at this time frame.

Short-term studies

The negative impact of neglect on short-term functional outcomes (within one year after stroke) in ADL is well established in the literature (for reviews, see Jehkonen et al., 2006; Stein et al., 2016).

Aphasia as a predictor of functional outcomes has also mainly been conducted during the short-term period. For example, seven studies that included aphasia but not neglect have investigated this relation with an end-point between 3-6 months after stroke. The studies were based on samples from: rehabilitation units (Gialanella, 2011; Gialanella, Bertolinelli, Lissi, & Prometti, 2011); retrospective stroke registers (Ali, Lyden, & Brady, 2013; Nesi et al., 2014); a hospital-based consecutive series (Pedersen et al., 1996); a community-survey (Wade et al., 1986) and a postal-questionnaire (Dalemans et al., 2010). One of these studies did not find a significant relationship between aphasia and unfavorable functional outcome (Pedersen et al., 1996) while the remaining studies reported such relation (Ali et al., 2013; Dalemans et al., 2010; Gialanella, 2011; Gialanella et al., 2011; Nesi et al., 2014; Wade et al., 1986).

There are also six short-term studies that investigated both neglect and aphasia. All but one of these studies found significant relationships with unfavorable functional outcomes for neglect but not for aphasia (Bickerton et al., 2015; Gialanella, Santoro, & Ferlucci, 2013; Nys et al., 2005; Paolucci., 1996, 1998). One found that both neglect and aphasia had a relationship with unfavorable functional outcome (Gialanella & Ferlucci, 2010).

In sum, this overview shows that there is relatively well-established literature of studies that investigated neglect and aphasia as early clinical predictors of unfavorable functional outcomes. However, most of these studies have been conducted during the short-term period i.e. within the first year after an acute stroke and it remains difficult to compare study findings because of variations in study designs, sample sizes, assessment methods, measures of functional outcomes at follow-up, and the timing of baseline and follow-up assessments (Jehkonen et al., 2006; Stein et al., 2016).

Long-term studies

Table 1 and 2 gives an overview of studies on stroke patients that investigated neglect and/or aphasia as possible predictors of long-term functional outcomes. In Table 1 details about each study are presented regarding the type of study, sample size, and statistical method used to analyze the data. Table 2 includes further information about assessment of neglect and/or aphasia at baseline, number of additional baseline variables, assessment at follow-up, and significant predictors of long-term functional outcome.

As seen in these two tables, there were three studies that included neglect (but not aphasia) in the investigation of possible predictors of long-term functional outcomes (Jehkonen et al., 2000, 2001; Katz, Hartman-Maier, Ring, & Soroker, 1999. All of these studies showed inferior outcomes for patients with neglect but the study by Jehkonen et al. (2001) showed that neglect was the most important single predictor of poor outcome but it had no additional value in combination with the other three predictors described in Table 2.

Three studies included aphasia (but not neglect) in the investigation of possible predictors (see Table 1 and 2; Bersano, Burgio, Gattinoni, & Candelise, 2009; Taub, Wolfe, Richardson, & Burney, 1994; Tsouli, Kyritsis, Tsagalis, Virvidaki, & Vemmos, 2009). In these studies, aphasia was significantly associated with unfavorable functional outcomes at follow-up (Table 2).

Six studies had included both neglect and aphasia as possible long-term predictors of functional outcome (Table 1 and 2; Appelros, Karlsson, Seiger, & Nydevik, 2003; Giaquinto et al., 1999; Lézniak, Bak, Czepiel, Seniów, & Członkowska, 2008; Paolucci et al., 2000, 2001; Young, Bogle, & Forster, 2001). Four of these studies identified neglect but not aphasia as a significant independent predictor of functional outcomes (Table 2; Appelros et al., 2003; Giaquinto et al., 1999; Paolucci et al., 2000; Young et al., 2001). One study found that patients with both neglect and aphasia had a higher probability of mobility decline compared to the other patients (Paolucci et al., 2001) and another study reported that neither neglect nor aphasia was significant predictors of poor functional outcome (Table 2; Leśniak et al., 2008).

Table 1. Long-term studies of functional outcomes following neglect/aphasia: Type of study, sample size, and statistical methods.

	Type of study	N (at follow-up)	Statistical method
Neglect (but not aphasia)[a]			
Jehkonen et al. (2000)	Hospital-based consecutive series of right hemisphere patients	50	Forward stepwise multiple regression
Jehkonen et al. (2001)	Hospital-based consecutive series of right hemisphere patients	49	Forward stepwise Cox regression model
Katz et al. (1999)	Rehabilitation unit-based	40	Stepwise multiple regression
Aphasia (but not neglect)[b]			
Bersano et al. (2009)	Hospital-based	8848	Multiple logistic regression
Taub et al. (1994)	Population-based	124	Forward and backward multiple logistic regression
Tsouli et al. (2009)	Prospective hospital-based	1603	Multiple logistic regression
Neglect & Aphasia[c]			
Appelros et al. (2003)	Population-based	253	Multiple logistic regression
Giaquinto et al. (1999)	Rehabilitation unit-based	217	Multiple regression
Paolucci et al. (2000)	Rehabilitaton unit-based	157	Forward stepwise multiple logistic regression
Young et al. (2001)	Hospital-based*	207	Forward, stepwise, and backward multiple regression
Paolucci et al. (2001)	Rehabilitation unit-based	141	Forward stepwise multiple logistic regression
Lésniak et al. (2008)	Hospital-based consecutive series of patients	80	Forward stepwise multiple logistic regression

*Recruited on hospital discharge or within 6 weeks post-stroke if not admitted to hospital (a sample from a previous study).
[a]Studies that included neglect but not aphasia; [b]studies that included aphasia but not neglect; [c]studies including both neglect and aphasia.

Table 2. Information about assessment at baseline, additional variables, assessment at follow-up, and significant predictors of functional outcome.

	Assessment at baseline (neglect and/or aphasia)	Number of additional baseline variables	Assessment at follow-up	Significant predictors
Neglect (but not aphasia)				
Jehkonen et al. (2000)	BIT < 10 days post-stroke	6	FAI 1 year post-stroke	Acute neglect in the behavioural subtests of BIT, age
Jehkonen et al. (2001)	BIT < 10 days post-stroke	9	Discharge to home 1 year post-stroke	Hemiparesis, unawareness of illness, presence of a relative
Katz et al. (1999)	BIT stroke-onset to rehab admission within the first 6 weeks	5	FIM & Rabideau Kitchen Evaluation 1 year post-stroke	Neglect, equilibrium in sitting, thinking operations, tactile sensation
Aphasia (but not neglect)				
Bersano et al. (2009)	Neurological examination by trained researcher neurologists as reported in the clinical records.	5	Dichotomized mRS 2 year post-stroke	Presence of aphasia
Taub et al. (1994)	Glasgow Scale < 24h after stroke-onset	9	Dichotomized BI 1 year post-stroke	Paralysis, urinary incontinence, speech problems, swallowing problems
Tsouli et al. (2009)	SSS < 24h after stroke-onset	7	Dichotomized mRS 1 year post-stroke	Severity of aphasia

Continued on next page

Table 2. (*continued)*

	Assessment at baseline (neglect and/or aphasia)	Number of additional baseline variables	Assessment at follow-up	Significant predictors
Neglect & Aphasia				
Appelros et al. (2003)	Neglect: BIT, BTT, and two tests of personal neglect. Aphasia: Language item from the NIHSS. 1–4 days post-stroke (in cases where patients were too ill, assessments took place within one month)	11	Katz ADL index and MMSE 1 year post-stroke	Post-stroke cognitive impairment, neglect, hemianopia, arm paresis, age
Giaquinto et al. (1999)	Neglect: Three levels of severity (Hemispheric Stroke Scale). Aphasia: Taylor Sarno Test. Stroke-onset to rehab admission - mean interval 23 days	10	FIM 1 year post-stroke	Age (years), cognitive and sphincter subitems of FIM-admission, neglect, ideomotor apraxia
Paolucci et al. (2000)	Neglect: Letter cancellation test, the barrage test, the sentence reading test, and the Wundt Jastrow area illusion test. Aphasia: Western Aphasia Battery. Stroke-onset to rehab admission - median 40 days	8	Dichotomized BI score 1 year after discharge from rehab	No postdischarge therapy, age ≥ 65 years, hemineglect
Young et al. (2001)	Neglect: Albert's test. Aphasia: Frenchay Aphasia Screening test.	28	Dichotomized FAI score 1 year post-stroke	Gait speed, prestroke FAI, abbreviated mental test score, sensory neglect, chronic obstructive airways disease, left hemiplegia
Paolucci et al. (2001)	Neglect: Letter cancellation test, the barrage test, the sentence reading test, and the Wundt Jastrow area illusion test. Aphasia: Western Aphasia Battery. Stroke-onset to rehab admission - median 40 days	9	RMI scores 1 year after discharge from rehab	Global aphasia, unilateral neglect, age ≥ 75 years
Lésniak et al. (2008)	Neglect: Line cancellation test from the BIT and the somatosensory extinction task. Aphasia: Language battery assessing spontaneous speech, repetition, naming, and comprehension as well as reading and writing abilities. 7-14 days post-stroke	18	Dichotomized BI 1 year post-stroke	Age (years), BI at 2nd week, executive dysfunction

BIT: Behavioural Inattention Test; SSS: Scandinavian Stroke Scale; BTT: Baking Tray Test; NIHSS: National Institutes of Health Stroke Scale; FAI: Frenchay Activities Index; FIM: Functional Independence Measure; BI: Barthel Index; mRS: modified Rankin Scale; MMSE: Mini Mental State Examination; RMI: Rivermead Mobility Index.

This overview of long-term studies that investigated neglect and/or aphasia as potential predictors of functional outcome once again shows the complexity of comparing study findings. Similar to the short-term studies previously presented, this complexity is due to the considerable variations between methodological choices and study designs, sample sizes, assessment methods of neglect and aphasia, measures of functional outcomes at follow-up, and the timing of baseline and follow-up assessments. Notably, despite these variations the majority of the long-term studies that investigated both neglect and aphasia has found an association with poor functional outcomes at one year post-stroke for baseline neglect but not for aphasia (Appelros et al., 2003; Giaquinto et al., 1999; Paolucci et al., 2000; Young et al., 2001) while two studies reported mixed results regarding this association (Leśniak et al., 2008; Paolucci et al., 2001).

Based on this overview of short- and long-term studies, the following conclusions could be made regarding the possible importance of baseline neglect and aphasia as predictors of functional outcome: 1) when aphasia (but not neglect) or neglect (but not aphasia) was investigated, each of them was identified as important correlates to functional outcomes, 2) when both aphasia and neglect were included in the same study the typical finding was that neglect but not aphasia was identified as an important correlate, and 3) there is an obvious lack of long-term studies exceeding one year after the baseline assessment.

The observation that the inclusion of neglect into the study seems to influence the importance of aphasia merits further investigations. One question that arises is if this effect is similar for patients with right and left hemispheric stroke. This question is motivated by the fact that aphasia is regarded as more common after a left hemispheric stroke and neglect as more common after right hemisphere stroke. However, it has been suggested that neglect may be rather common also after a left hemisphere stroke, at least at the acute phase (Murray, 2002; Hreha et al., 2016; Suchan, Rorden, & Karnath, 2012). It has also been suggested that the reported incidence of both neglect and aphasia after a stroke may be biased since patients with severe aphasia often are excluded in stroke studies due to reduced comprehension (Hreha et al., 2016; Suchan et al., 2012). Thus, in investigations of the possible effects of baseline neglect and aphasia it is important to obtain data also from the patients with severe acute language symptoms. Finally, the investigation of the influence of both neglect and aphasia in the same study is important since several recent studies have indicated that impaired attention together with aphasia may influence the impact and progress of aphasia (Murray, 2002).

The terms lateralized and non-lateralized visual inattention

A typical sign of spatial neglect is an abnormal asymmetry in the allocation of attention and motor responses in space (Heilman, Watson, & Valenstein, 1985). In the studies of the present thesis an abnormal asymmetric performance in test(s) of visual target cancellation was regarded as a sign of neglect and it was termed *lateralized visual inattention.* Thus, in these studies, this term simply stands for presence of lateralized signs of neglect in visual target cancellation and the term was used in order to signal that all aspects of the neglect syndrome was not covered by this measure. This thesis does not involve discrimination between different subtypes of neglect. Instead, a main objective was to investigate if rather simple clinical tests and observations at the early stage after stroke can obtain useful prognostic information. When a visual target cancellation test is used to identify asymmetric signs of neglect some participants will exhibit omissions of targets that are symmetrically distributed between the two sides of the test sheet. This type of omissions was not considered as lateralized neglect, although it still is a sign of visual inattention, and it was termed *non-lateralized visual inattention* in this thesis. It should be noticed that, although a non-asymmetric inattention in target cancellation was not regarded as neglect, it may be a rather common observation in the later stage among individuals who have improved from the lateralized signs of neglect (Samuelsson, Hjelmquist, Jensen, & Blomstrand, 2002). It should also be noticed that patients with asymmetric signs of neglect in target cancellation also may have general not spatially lateralized impairments, for instance in alertness or sustained attention (Robertson, 2001). That is, patients defined as having signs of neglect by the use of the term lateralized visual inattention may at the same time have other non-lateralized impairments and within the complex neglect phenomenon there are probably different overlapping impairments and dysfunctions.

The term *visuospatial inattention* was used in this thesis as an umbrella term for both lateralized and non-lateralized visual inattention. The overall severity of visuospatial inattention, regardless of the presence of asymmetry or not, was also described in this thesis – it was given as the total number of omissions in the target cancellation test(s).

Processing speed after stroke

Processing speed (PS) or information processing speed can be defined as the number of correct responses or quantity of work completed within a given time limit or as the time taken to accomplish a certain task (Costa, Genova, Deluca, & Chiaravalloti, 2017; Sweet, 2011). The association between PS, the aging process, and disease-related changes in cognitive abilities has been widely studied (Kail & Salthouse, 1994; Salthouse, 1996) in both young and old participants, as well as in clinical groups and healthy controls (Su, Wuang, Lin, & Su, 2015). For example, the underlying role of PS in cognitive dysfunction within domains such as attention and/or visuospatial function has been reported in studies of traumatic brain injury (Willmott, Ponsford, Hocking, & Schönberger, 2009), multiple sclerosis (Diamond, Johnson, Kaufman, & Graves, 2008), and dementia (Rizzo, Anderson, Dawson, Myers, & Ball, 2000).

Cognitive impairment is common after stroke and decreased PS has been proposed as among the most severe cognitive deficits after stroke (Barker-Collo et al., 2010). Others have showed that decreased PS underlies decline in cognitive domains such as visuospatial attention and executive function (Su et al., 2015; Winkens, van Heugten, Fasotti, Duits, & Wade, 2006). In a study by Schaapsmerders et al. (2013) a consecutive series of 277 young ischemic stroke patients aged 18-50 years completed cognitive assessments 11 years post-stroke. They found that a large proportion of patients had cognitive impairments at follow-up and deficits in PS, working memory, and attention were most common.

PS has been identified as an independent correlate to long-term functional outcome (Barker-Collo et al., 2010; Viken et al., 2014). One study by Barker-Collo et al. (2010) consisted of a population-based sample of 307 patients, and it was a cross-sectional study conducted 5 years after stroke. The study investigated associations between different neuropsychological deficits such as in PS, visuoperceptual ability, and executive function and measures of functional outcomes on handicap and disability. They found that impaired PS was among the most common deficit and independently associated with the functional outcomes after adjusting for age, depression, and stroke severity. Another cross-sectional study by Synhaeve et al. (2015) examined the influence of cognitive performance on long-term functional outcome in 277 younger ischemic stroke patients recruited from a prospective cohort. At follow-up 11 years after stroke, no relation was found between cognitive deficits and long-term functional outcome in Instrumental Activities of Daily Living (IADL) except for deficits in PS and working memory. Viken et al. (2014) investigated a consecutive series of 105 right hemispheric stroke patients that were tested early after stroke for different symptoms of visuospatial neglect and processing speed. Functional outcome was measured with the modified Rankin Scale (mRS) at 3 months and at 2 years after stroke onset. This study found that PS early after stroke was the most important predictor for dependency (mRS score >2) but only at the 2-year follow-up.

In a recent longitudinal study by Nurmi et al. (2018) a relationship was found between neglect-related symptoms and slowed PS at the acute phase, at six months, and at one year after stroke. In another study by Rasquin, Verhey, Lousberg, Winkens, and Lodder (2002) the occurrence of cognitive disorders in memory, basic speed, cognitive flexibility, and in overall performance were investigated at 1 and 6 months post-stroke and they found that on all cognitive domains, except for speed, most patients improved at 6 months compared to their baseline scores. Comijs et al. (2009) examined the longitudinal association between specific chronic diseases and cognitive functioning in a large population-based sample (aged 62-85 years) and found that occurrence of stroke was associated with a significant decline in PS and memory at a 6 year follow-up.

The investigation described above indicates a decline in PS at the late stage after stroke and a relationship with poor long-term functional outcome. Despite the evidence, there are few longitudinal studies that examine the changes in PS several years after stroke and possible associations with cognitive impairments and functional outcome.

The definition of PS given above is rather wide. In an attempt to make the description of PS more useful a tri-factor model was suggested in a recent review of PS following multiple sclerosis (Costa et al., 2017). It was stated that PS includes three levels of processing: sensorial, cognitive, and motor and that the type of processing that is investigated can be described based on these three levels. In the present thesis a target cancellation task was used for the measure of PS. Based on the tri-factor model and the definition given above, the PS investigated in the present thesis can be defined as the number of correct responses completed within a given time limit, including processing at a sensorial (vision and simple perception), cognitive (orientation of visuospatial attention and visual search), and motor (manual cancelling) level. In addition, it can be described as a relatively simple task. The overall speed score was used in the present thesis and no attempt was made to separate individual contributions to the score by the different levels (sensorial, cognitive, and motor) of the measurement. It can be considered as a global marker of the speed of processing.

AIMS OF THE STUDIES

Study I

The aim of study I was motivated by the lack of long-term studies exceeding one year and the finding that the inclusion of both neglect and aphasia into the same study probably affect the type of outcome.

The main aim was to investigate if identification of basic signs of neglect and aphasia at the acute phase could provide prognostic information about the functional outcome (i.e. disability and levels of participation in instrumental activities of daily living) 7 years after the index stroke. We hypothesized that neglect and aphasia could predict the outcome.

Study II

The aim of study II was motivated by 1) the observations made in study I that stroke laterality was not related to the outcome which indicated that VSI might provide information of long-term functional outcome following a left hemispheric stroke and 2) the findings in the literature that the incidence of neglect after a left hemispheric stroke may be biased as patients with severe aphasia often are excluded due to reduced comprehension.

The aim was to investigate to what extent VSI is a predictor of long-term functional outcome for patients with a left hemispheric stroke, also including patients with severe language impairments. We hypothesized that: 1) an early basic classification of VSI after a left hemispheric stroke can provide prognostic information about long-term functional outcome, 2) a combination of impairments in visuospatial attention and language is associated with worse functional outcome, and 3) the potential importance of VSI as a predictor of functional outcome is decreased if those unable to perform conventional tests are not included.

Study III

Study III was motivated by the fact that there are almost no studies on unselected stroke cohorts that describe presence of lateralized inattention in the long-term perspective, many years after stroke. Most studies have been conducted within the first year and studies beyond the first year typically comprised rather small selective subgroups of right hemispheric stroke patients.

The aim was to investigate long-term presence of lateralized inattention 7 years post-stroke in an unselected cohort and identify baseline predictors for presence of these symptoms.

Study IV

The motive behind study IV was the reports that processing speed is an important component behind cognitive and functional outcome and the lack of knowledge in the stroke literature about long-term changes in processing speed. Increased knowledge about this pattern of change can hopefully guide future investigations about the relations between stroke and processing speed in the long-term.

The study aimed to describe: 1) the patterns of change in PS across three time points, 2) the ecological validity of PS in terms of the associations with functional outcome, and 3) the association between PS and age, and 4) to describe change in PS with change in visuospatial inattention and neurological deficits.

The studies focused on a cohort of relatively young stroke survivors (<70 years at index stroke). Knowledge of long-term outcomes in this group of individuals is of specific importance, as they have long life expectancy and may live many years with stroke-related consequences during a period normally devoted to an active life. In addition, it is important to both increase our knowledge about the possible impact of attentional deficits in individuals with left hemisphere stroke and aphasia and its relation with long-term functional outcomes. It is also important to increase our knowledge about potential baseline predictors for signs of lateralized inattention in the long-term after stroke and the relation between change in processing speed across time and functional outcome. Reliable information about the long-term prognosis is of importance, not only for the affected individuals and families, but also for the design of long-term intervention and support programs.

SUMMARY OF THE STUDIES

Methods

Participants

The participants in studies I-IV were from the Sahlgrenska Academy Study on Ischemic Stroke (SAHLSIS). SAHLSIS is a longitudinal study of ischemic stroke in the young and middle-aged adults, for which the details have been described elsewhere (Jood, Ladenvall, Rosengren, Blomstrand, & Jern, 2005). In brief, from August 1998, patients who presented with first-ever or a recurrent acute ischemic stroke between ages 18 and 69 were consecutively recruited at stroke units in Western Sweden. Ischemic stroke was defined according to WHO criteria. In Sweden, a universal health care system is provided to all citizens, and according to national guidelines all patients with acute symptoms indicating stroke should be hospitalized, and thus patients recruited at stroke units are representative for the stroke population. The inclusion criteria were: (i) acute onset of clinical symptoms of suggestive stroke and (ii) no hemorrhage on magnetic resonance imaging (MRI) or computed tomography (CT) scan of the brain. Patients were excluded if: (i) the symptoms resolved completely within 24 hours, (ii) an etiology other than ischemic stroke was found, and (iii) they had a diagnosis of cancer at an advanced stage, infectious hepatitis, or HIV.

The present studies comprised the SAHLSIS participants who were recruited at the Stroke Unit at the Sahlgrenska University Hospital between August 1998 and December 2003. They were investigated within the first 1-7 days or as soon as possible after the first 7 days, at 3 months (study IV), and at 7 years after stroke. Only participants with a 7-year follow-up and with no recurrent stroke during follow-up were included in the present investigations. Recurrent strokes were identified by medical history at the 7-year visit, by search in medical records, and by using the National Inpatient Register (IPR) as described (Redfors et al., 2012).

In study I, a consecutive series of 375 subjects were recruited regardless of the location of the brain lesion. Of these, 235 participants were investigated at the 7-year follow-up and were included in the study. Reasons for those lost to follow-up are given in Figure 1.

In study II, only patients with a left hemispheric stroke were included. Of these, 4 patients had additional signs of infratentorial lesions. All patients with right hemispheric stroke, involvement of both hemispheres, or infratentorial lesions with no supratentorial involvement were excluded (Figure 1). These exclusions were based on the information from the CT/MRI and neurological clinical symptoms described in the medical records, reviewed by a neurologist (KJ). After these exclusions, 105 participants remained for analysis (Figure 1). For more details of participants lost to follow-up, see Figure 1 in study II in appendix**.** Studies I-II started at the stage in the SAHLSIS when the Star Cancellation Test was introduced. At this stage only one test of neglect (Star Cancellation Test) was used, no additional tests of processing speed or target cancellations were used at this point.

Studies III-IV started at a later stage of SAHLSIS when additional tests of processing speed and target cancellations were included. These studies consisted of a consecutive series of patients starting at the first patient with these additional assessments (Figure 1), resulting in 297 eligible patients. In study III after exclusions, according to the same criteria as in studies I-II, 188 subjects were included. In study IV, only participants who had data on processing speed and target cancellations from three different time points (baseline, 3 months, and 7 years) were included, resulting in 148 included participants. For more details of those lost to follow-up, see Figure 1.

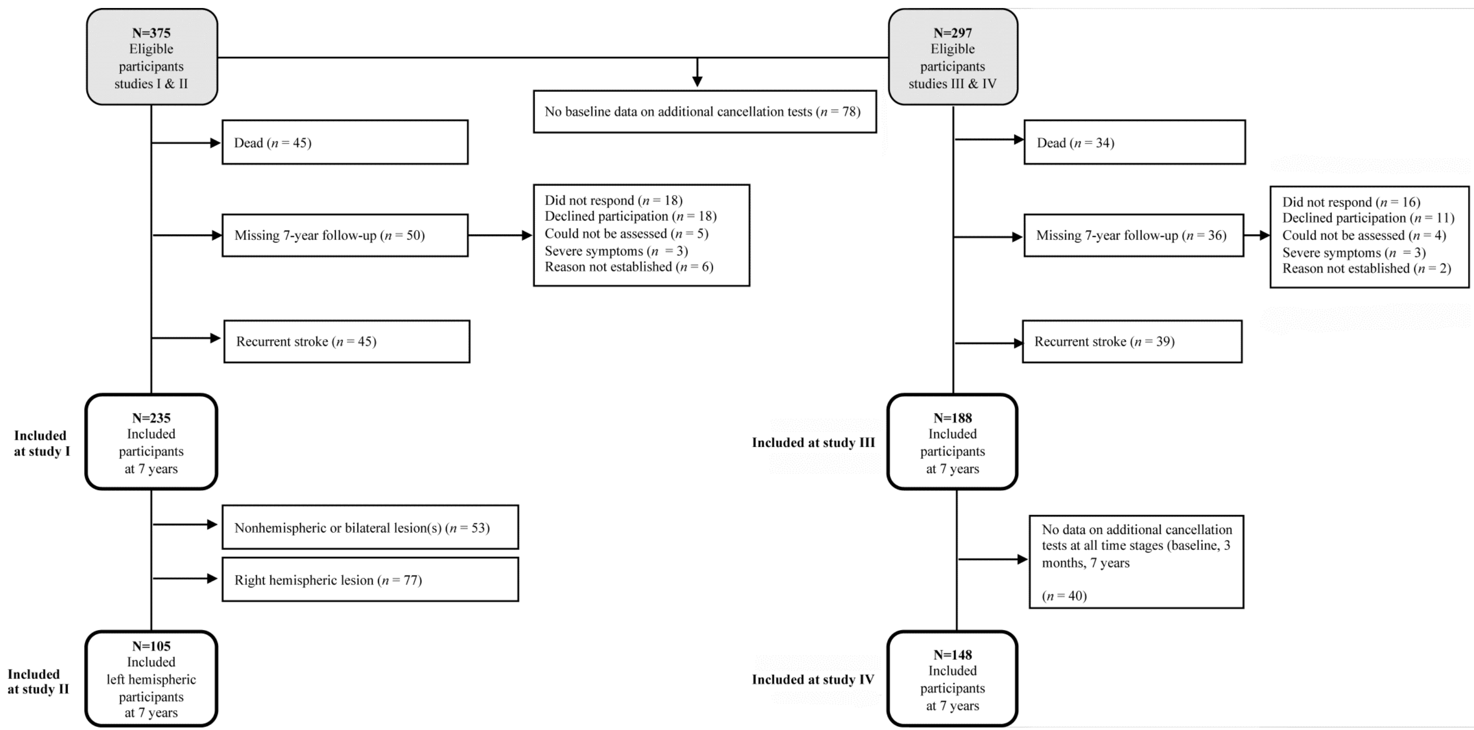

Figure 1. Flowchart of eligible participants in studies I-IV and reasons for exclusions.

Variables and tests

Assessments from the early stage post-stroke (the baseline assessments) of visuospatial inattention, language impairment, PS, and other neurological deficits were administered by a neurologist and a research assistant. In studies I-III the assessments were made at median 7 days (interquartile range 5 days) after admission to the hospital for visuospatial inattention, and within the first 7 days post-stroke for the Scandinavian Stroke Scale (SSS) (studies I-IV). In study IV the assessment of visuospatial inattention was made at median 6 days (interquartile range 4 days) after the index stroke.

Demographics (studies I-IV)

Age was assessed in whole years and sex as female or male. In study III, education was dichotomized as ≤9 years, and >9 years, following the Swedish educational system in which 9 years of school is mandatory. Data about education was collected at the 7-year follow-up.

Classification of visuospatial inattention (VSI)

Studies I-II

The classification of presence of VSI at baseline included both asymmetric neglect and non-asymmetric inattention and was assessed with the Star Cancellation Test (SCT). It is a conventional paper and pencil subtest of the normalized and standardized Behavioral Inattention Test (BIT; Wilson, Cockburn, and Halligan, 1987) with a total score of 54. This battery has shown good reliability (Halligan, Cockburn, & Wilson, 1991). Patients are instructed to cancel 54 targets (small stars) among several distractors (letters, short words, and large stars). Twenty-seven targets are located at each side of the test sheet. Two small stars in the mid-line of the test were used to demonstrate the cancellation procedure. Patients were classified into three levels of VSI according to their performance in the test in terms of detected targets: *Lateralized visual inattention;* omission of at least three more targets at one half of the SCT sheet, *Non-lateralized visual inattention;* total score ≤ 52 and not fulfilling criteria for LVI, *No visual inattention;* A total score > 52.

In study II the following abbreviations of the three VSI groups were used: LVI (lateralized visual inattention), NLVI (non-lateralized visual inattention), and No VI (no visual inattention).

Study IV

In study IV the classification of VSI was based on both the SCT and Letter Cancellation Test (LCT). The LCT has 40 targets consisting of the letters “E” and “R” spread among distracter letters. A timed version of the test was used and the patient was instructed to perform the test as fast and accurately as possible. Patients were classified into three levels according to their performance in the tests: *LVI;* a score below cut-off (≤ 52 on the SCT or < 37 on the LCT) and with omission of at least three more targets at one half of the SCT or LCT sheets, *NLVI;*

total score ≤ 52 on the SCT or < 37 on the LCT and not fulfilling criteria for LVI, *No VI;* a total score above cut-off on both tests. In studies I-II and IV the cut-off levels in the SCT and LCT were based on the performance of 25 controls (median: 57 years, range: 29-70 years) from a previous study (Samuelsson, Hjelmquist, Naver, & Blomstrand, 1995).

Language impairment (LI) (studies I-II)

The language item of the SSS (Boysen, 1992) was used to assess the degree of language impairment after stroke in three groups: *Severe language impairment (SLI).* The patient only produces yes/no or less - or the patient produces more than yes/no, but no longer sentences. *Mild language impairment (MLI).* Limited vocabulary, or incoherent speech. *No language impairment (No LI).* No signs of aphasia. The validity of the SSS language item has been investigated (Thommessen, Thoresen, Bautz-Holter, & Laake, 2002) where the assessment was carried out by a nurse with a parallel full evaluation report from a speech therapist. The agreement between the nurse's and the speech therapist's score as well as the sensitivity and specificity of the item was satisfactory. However, it was found that using the SSS language item as a diagnostic tool results in high rates of type I-errors (false positives) and thus overestimates the prevalence of language impairments.

Therefore, in order to try to limit the risk of false positives, in study I, the language impairments were validated against the medical records for all participants who according to SSS had language impairment combined with either decreased level of consciousness or facial palsy. This was made since these additional symptoms can make it difficult to discriminate between presence and absence of aphasic symptoms. In study II, this validation against the medical records was further extended to all participants with language impairment according to the SSS. This validation procedure was based on the clinical symptoms described in the medical records from the admission to the Stroke Unit and during the initial period at the unit. In most cases, the information was based on the speech therapists' reports. In study I, this procedure resulted in reclassification of language impairment in 8 participants as No LI and in study II there were 2 additional participants reclassified as No LI. For more details see supplementary information Table S2 in study II in appendix.

Retrospective classification (VSI) (studies I-II)

In order to reduce bias through exclusions at the early phase, patients who could not be tested with the SCT described above were retrospectively classified regarding VSI by a neurologist (C.B.) (study I) and independently by two neurologists (C.B. and K.J.) (study II). The classifications were based on clinical symptoms described in the medical records during the stay at the Stroke Unit, including reports from physical and occupational therapists and neuropsychologist's reports when applicable.

There was full agreement between the independent judgements for 22 of 28 patients (78.6%) with 8 judged as LVI and 14 as No VI. For six participants consensus was reached after discussion. Three of these were classified as LVI, one as No VI, and two as not possible to classify. The main reasons for the initial disagreement regarding these six cases were a fast remission of signs of inattention after the stroke event, lowered consciousness and/or confounding medical complications at the early stage post-stroke. For the two patients judged as not possible to classify, the reasons were that the records did not contain any clear description of the attentional state and especially so for participants with lowered awareness at the regain of awareness.

Total omissions in target cancellations (study III)

The total number of omissions was assessed by the two paper-and-pencil tests SCT and LCT. For each of the two cancellation tests the number of omissions was calculated and divided by the tests' maximum total score multiplied by hundred. The mean value from these two scores was used as the mean percentage score of total omissions and reflects the overall severity of visuospatial inattention.

Omission asymmetry in target cancellations (study III)

The omission asymmetry was calculated for the SCT and the LCT by subtracting the number of omissions on the left side from those at the right side on the test sheet. Negative scores from these calculations were transformed into absolute scores. For each of the two cancellation tests the number of absolute omission asymmetry was divided by the tests' maximum asymmetry score multiplied by hundred. The mean value from these two scores was used as the mean percentage score of omission asymmetry and represents an overall score of asymmetry in the performance.

Processing speed (study III)

A mirrored copy of the test sheet from the SCT described above was used and administered with a time limit of 30 seconds (SCT [30 sec]). The patients were asked to cross out as many targets as they could find within the time limit. The total number of correct cancellations during the time limit was used as a measure of processing speed.

Stroke severity

Stroke severity was assessed by the Scandinavian Stroke Scale (SSS) (Boysen, 1992). It is used to assess overall severity of neurological deficits after stroke and good reliability has been reported for this scale (Lindenstrøm, Boysen, Christiansen, Hansen, & Nielsen, 1991). The total score ranges from 0 (no physical functioning ability) to 58 (complete physical functional ability). In studies I-II the sub-item language was used as a separate variable to classify LI. In study II this item was excluded from the total SSS score, resulting in the total score of 48 and consisted of the eight remaining sub-items (consciousness, eye movement, arm-, hand-, and leg-strength, facial palsy, orientation for time, place, and person, and ability to walk). In study I analyses were made using both versions of the SSS: the full SSS (score 0-

58) and the SSS without the language sub-item (score 0-48). The full SSS (score 0-58) was used in study III.

Visual field deficit (VFD) (studies I-III)

VFD was investigated during the acute/subacute phase after index stroke and classified as either present or absent using conventional confrontation techniques. For those who could not be classified for VFD the classification was based on retrospective information from the medical records, examined by a neurologist (C.B.).

Lesion location (studies I-IV)

All included participants had a brain computed tomography (CT) examination and in study I, 215 (91.5%) underwent brain magnetic resonance imaging (MRI). The number of participants with an MRI examination were 96 (91.5 %) in study II, 169 (89.9 %) in study III, and 135 (91.2 %) in study IV. A neurologist (K.J.) reviewed the patients' CT/MRI reports and classified acute stroke lesion as supratentorial (left, right), infratentorial, or multiple lesions. Previous vascular lesions (old brain infarcts) were also documented. In participants for whom CT and/or MRI did not visualize the acute stroke, the location of the lesion was based on the clinical symptoms.

Side of clinical symptoms (study I)

The neurological clinical symptoms described in the medical records were classified by a neurologist (K.J) as either left or right-sided or as non-asymmetric.

Stroke subtype (studies I-III)

The Oxfordshire Community Stroke Project (OCSP) classification criteria (Bamford, Sandercock, Dennis, Burn, & Warlow, 1991) was used. This classification of vascular supply area was done by a neurologist (K.J.) by reviewing medical records. If a classification was uncertain, the judgement was made in consensus by two neurologists (K.J. and C.B.). The OCSP is considered to have satisfactory reliability and reasonable validity in establishing general site and size of the vascular territory of infarction (Lindley et al., 1993; Wardlaw, Dennis, Lindley, Sellar, & Warlow, 1996). Strokes were either classified as lacunar infarcts (LACI), total anterior circulation infarcts (TACI), partial anterior circulation infarcts (PACI), posterior circulation infarcts (POCI), or infarcts not possible to classify.

Cardiovascular risk factors (studies I and III)

Data on cardiovascular risk factors were collected at inclusion and at a 3-month follow-up visit, and our definitions of hypertension, diabetes mellitus, hyperlipidemia, and smoking have been described in detail elsewhere (Jood et al., 2005). These risk factors were scored as present or not present.

Assessments conducted at baseline, 3 months, and at 7 years (study IV)

In study IV, data were collected at baseline, 3 months, and at the 7-year follow-up from the following measures described above.

Age
Processing speed (SCT 30 sec)
Stroke severity

Processing speed
In study IV the cut-off levels for impaired performance were set at a score one point below the lowest score in a control group of similar age range. The cut-off levels were a score <40 for the baseline and 3 month assessments and <39 at the 7-year follow-up. The cut-off for the 7-year follow-up was based on the performance of 34 controls (median 66 years; range 29-75 years, 17 (50 %) female) consisting of neurologically healthy participants from a previous study (Samuelsson, 1997; Samuelsson et al., 1995) and the cut-offs for baseline and 3 months were based on a subsample of 25 subjects from the same control group but with max age of 70 years (median 57 years; range 29-70 years, 12 (48 %) female).

Stroke severity
Stroke severity was assessed with the SSS at baseline and at 3 months and neurological deficits with the National Institutes of Health Stroke Scale (NIHSS; Brott et al., 1989) at the 7-year follow-up. In order to make these scales comparable, the SSS scores at baseline and at 3 months were converted to NIHSS scores by a mathematical equation (Gray, Ali, Lyden, & Bath, 2009). The NIHSS score ranges between 0 and 42, where higher scores indicate more impairment. The scale comprises 15-items and assesses neurological deficits in different functions caused by stroke.

Total target cancellations in tests without a time limit
In study IV, comparisons between numbers of cancellations of targets in tests with and without a time limit were made. The total sum of correct cancellations from the SCT and LCT (described above) was used to describe the performance and changes across time in cancellation tests without a time limit.

Outcomes at the 7-year follow-up

Studies I-II
Functional outcomes 7 years after the index stroke were assessed with modified Rankin Scale (mRS; Bonita & Beaglehole, 1988) and the Frenchay Activities Index (FAI; Holbrook & Skilbeck, 1983). The mRS (Bonita & Beaglehole, 1988) is an ordinal disability scale shown

to have acceptable validity and reliability (Banks & Marotta, 2007; D'Olhaberriague, Litvan, Mitsias, & Mansbach, 1996; van Swieten, Koudstaal, Visser, Schouten, & Van Gijn, 1988). It describes surviving patients' general dependency level on a scale ranging from 0 (no symptoms at all) to 5 (severe disability, requiring constant care and attention). Assessments of mRS were performed by a trained study nurse at a study visit 7 years after stroke. Patients who were unable to visit our clinic were offered a home visit.

The FAI (Hoolbrook & Skilbeck, 1983) is considered a valid and reliable stroke-specific instrument (Green, Forster, & Young, 2001; Post & de Witte, 2003; Schuling, de Haan, Limburg, & Groenier, 1993). It is used to assess instrumental activities of daily living (IADL), based on the frequency of performance in activities with regard to domestic, leisure/work, and outdoor activities. The FAI consists of 15 items and each item is scored on a four-point scale from 0 (the lowest level of activity) to 3 (the highest level of activity). The total score of the scale was used in these studies ranging from 0 to 45 (Jansen, Schepers, Visser-Meily, & Post, 2012; Patel et al., 2006). The FAI questionnaire was posted to the participants before the study visit, and the research nurse made a check-up of the ratings at the visit.

Study III

The outcome in this study was based on the classification of lateralized inattention that was made at median 7 years and 5 months (interquartile range 3 months) after index stroke. Lateralized inattention was assessed by the SCT and LCT and with the extinction/neglect item of the NIHSS. For the cancellation tests the cut-off for impaired performance for participants aged ≤ 69 years was a total score ≤ 52 on the SCT and < 37 on the LCT, and the cut-off levels for those > 69 years were a total score < 52 on the SCT and < 34 on the LCT. These levels were based on the performance of 34 controls (median, 66 years; range, 29-75 years) from a previous study (Samuelsson et al., 1995). The scores (0-2) on the NIHSS item were: 0 (none), 1 (mild), 2 (profound). According to the cancellation tests and the NIHSS, participants were classified into one of the following two groups at follow-up: (i) *Lateralized inattention*, a score below cut-off and with omission of at least three more targets at one half of the sheet for any of the two cancellation tests, and/or a score > 0 on the neglect item of NIHSS; (ii) *No lateralized inattention*, not fulfilling the criteria above for lateralized inattention based on the cut-offs of the cancellation tests and the neglect item of NIHSS.

Study IV

Outcomes at 7 years were mRS, FAI, and the recovery item of Stroke Impact Scale (SIS; Duncan et al., 1999). The SIS is a stroke-specific, self-reported, health status measure. One of the items in the SIS is a visual analog scale of 0 to 100 and the patients are asked to rate their perceived percent recovery since stroke on this scale, where 0 means no recovery and 100 full recovery. In this study, this recovery item of SIS was used.

Statistical analyses

Studies I-IV

Multiple group comparisons with additional two-group comparisons were made with non-parametric statistics. Kruskal-Wallis one-way analysis of variance (continuous data) and Chi-square (categorical data) were used for analyses of overall group differences. Post-hoc two-group comparisons were performed with Mann-Whitney *U* test (continuous data) and Fisher's exact test (categorical data). Monte-Carlo or Exact methods were selected accordingly depending on the group sizes, for computation of the *p*-values. An alpha level $\leq .05$ was used. All analyses were performed with IBM SPSS Statistics, Version 21.0 (study I) and 24.0 (studies II-IV) and JMP® Pro, Version *13*. SAS Institute Inc., Cary, NC, 1989-2007 (study III). For details regarding statistical methods, please refer to the respective papers.

Studies I-II

Analyses of possible baseline predictors of functional outcome were made with Spearman's rank-order correlation (*Rho*) and multivariable categorical regression. Spearman's rank-order correlation was performed between baseline predictors and the total score for each of the two outcome variables. Predictors with a correlation coefficient with a value $\geq .15$ were selected for a further multivariable regression analysis. VSI and LI were selected for the multivariable regressions regardless of their level of the bivariate correlation. At the multivariable regression analyses, patients with missing data were excluded. For all two-group comparisons in study I, Bonferroni-Hochberg corrections for multiple comparisons were performed.

Study III

Possible baseline predictors of long-term signs of lateralized inattention were analyzed with two-group comparisons and with multivariable binominal generalized regression. At the two-group analyses baseline scores were compared between participants with no lateralized inattention and those with lateralized inattention at follow-up. Effect sizes based on the Mann-Whitney *U* tests were given as a Pearson's *r* and obtained by the formula: $Z / \sqrt{N}$. Effect sizes of the Chi-square and Fisher's exact tests were based on the Phi coefficient (φ) which is similar to the Pearson's *r* in its interpretation (Field, 2005). The interpretation of effect sizes were: .10 (small), .30 (medium), and .50 (large) (Cohen, 1988). For the regression analysis the shrinkage and selection method lasso was used.

Study IV

Analyses of bivariate associations between processing speed, functional outcome, and age were analyzed with Spearman's rank-order correlation (*Rho*). Partial Spearman's correlations were used for analyzing associations between processing speed and functional outcome when adjusting for age. Overall within-group differences were analyzed with the Friedman's test and post-hoc two-group comparisons (within-groups) with Wilcoxon signed-rank test.

Results

Study I

In study I, 235 individuals were investigated at baseline and at the 7-year follow-up. At the early assessment, 28 with missing data on VSI were retrospectively classified based on the medical records as lateralized visual inattention (*n* = 9), visual inattention (*n* = 2), and no visual inattention (*n* = 15). Four participants with missing data on language impairment were retrospectively classified as no language impairment.

Baseline predictors of functional outcome

Bivariate correlations between baseline predictors and functional outcome at follow-up are shown in Table 3. The baseline scores are correlated with the total scores from mRS and FAI. For the outcome in mRS, an absolute correlation coefficient ≥ .15 was observed for visuospatial inattention, language impairment, for those who were retrospectively classified, SSS, TACI, and POCI. For the outcome variable FAI, bivariate correlations ≥ .15 were observed for age, visuospatial inattention, for those who were retrospectively classified, SSS, TACI, and diabetes mellitus.

Table 3. Correlations between baseline assessments and functional outcome (mRS and FAI) at 7 years after index stroke.

	mRS at 7 years	FAI at 7 years
	Rho	*Rho*
Baseline variable		
Age (years)	.06	-.20**
Females	.04	.09
Visuospatial inattention[a,b]	-.35**	.30**
Language impairment[a]	-.21**	.11
Retrospectively classified for VSI or LI[c]	.22**	-.22**
Neurological deficits		
SSS score without language item[d]	-.42**	.32**
Visual field deficit	.08	-.06
CT/MRI results		
Localization of index stroke lesion		
Left/Right hemisphere	.03	.05
Old brain infarcts	.02	-.06
Clinical symptoms		
Left/Right-sided	-.02	-.04
The Oxford Project Stroke Classification		
LACI	-.09	.03
TACI	.38**	-.28**
PACI	.03	.07
POCI	-.18**	.10
Not possible to classify[e]	-	-
Cardiovascular risk factors (yes)		
Hypertension	.01	-.02
Diabetes mellitus	.13	-.25
Hyperlipidemia	.08	.02
Smoking	.03	-.09

Test statistics: The bivariate *Rho* was computed between the total outcome score and baseline scores or between the total outcome score and the two-level dichotomized baseline score. mRS, modified Rankin Scale; FAI, Frenchay Activities Index; SSS, Scandinavian Stroke Scale; LACI, lacunar infarct; TACI, total anterior circulation infarct; PACI, partial anterior circulation infarct; POCI, posterior circulation infarct. [a]Visuospatial inattention was coded into three ordinal levels; Lateralized visual inattention (1), Visual inattention (2), No visual inattention (3). Language impairment was coded into three ordinal levels; Severe language impairment (1), Mild language impairment (2), No language impairment (3). [b]Two patients who did not perform the SCT could not be retrospectively classified for visuospatial inattention. [c]Patients who did not perform the SCT or SSS at baseline were retrospectively classified for the presence of visuospatial inattention and language impairment .

[d]Seven patients did not have a total score in SSS. [e]Three patients were not possible to classify. Number of patients without assessment on FAI: 1. **$P < .01$ (2-tailed).

All predictors with an absolute correlation coefficient ≥ .15 with mRS and FAI in Table 3 were further analyzed in a multivariable regression for each outcome. Table 4 shows the statistically significant predictors in each model. The importance given in the table indicates the relative contribution of each predictor to the model (in percentage).

Table 4. Significant predictors of mRS and FAI at 7 years.

	Standardized coefficients		Importance	*df*	*F*	*P*
	B	SE				
Outcome: modified Rankin Scale (mRS)						
Visuospatial inattention	-0.306	0.112	0.370	2	7.455	**.001**
Retrospectively classified for VSI or LI	0.163	0.081	0.120	1	4.056	**.045**
SSS score without language item	-0.308	0.069	0.351	2	19.947	**< .001**
Outcome: Frenchay Activities Index (FAI)						
Visuospatial inattention	0.173	0.094	0.227	2	3.154	**.035**
SSS score without language item	0.294	0.076	0.458	2	18.092	**< .001**

The model for mRS**:** $\boldsymbol{R^2}$ = 0.435, **F =** 18.213, **df = 9, P** < .001, **Adjusted** $\boldsymbol{R^2}$ **=** .411

The model for FAI**:** $\boldsymbol{R^2}$ = 0.269, **F** = 7.750, **df** = 10, **P** < .001, **Adjusted** $\boldsymbol{R^2}$ = .234

Study II

In study II, 105 individuals with left hemispheric stroke were investigated at baseline and at the 7-year follow-up. As shown in Table 5, presence of language impairment was observed in 38 (36.2 %) individuals (17 severe and 21 mild impairments) and visuospatial inattention in 23 (22.1 %, 10 lateralized and 13 non-lateralized visual inattention). In 12 participants (11.4 %) impairments of visuospatial attention and/or language were retrospectively classified (11 for visuospatial inattention, 1 for both visuospatial inattention and language impairments).

Table 5. Presence of visuospatial inattention, language impairment, and retrospectively classified individuals.

Baseline assessments	N = 105
Visuospatial inattention	
Lateralized visual inattention, n (%)	10 (9.6)
Non-lateralized visual inattention, n (%)	13 (12.5)
No visual inattention, n (%)	81 (77.9)
Language impairment	
Severe language impairment, n (%)	17 (16.2)
Mild language impairment, n (%)	21 (20.0)
No language impairment, n (%)	67 (63.8)
Retrospectively classified for VSI or LI, n (%)	12 (11.4)

Missing data: One patient who did not perform the SCT could not be retrospectively classified for VSI.

Baseline predictors of functional outcome

Bivariate correlations between baseline predictors and total outcome scores at follow-up are presented in Table 6. For the outcome variable mRS, a correlation coefficient ≥ .15 was observed for visuospatial inattention, language impairment, for those who were retrospectively classified, SSS, and visual field deficit. All these predictors except visual field deficit were also associated with the outcome variable FAI with a correlation coefficient ≥ .15.

Table 6. Correlations between baseline assessments and functional outcome (mRS and FAI) at 7 years after index stroke.

	Outcomes at 7 years	
	mRS	FAI
	Rho	*Rho*
Baseline variables		
Age in years	.10	-.10
Females	.10	.02
Visuospatial inattention[a,b]	-.50**	.45**
Language impairment[a]	-.39**	.28*
Retrospectively classified for VSI or LI[c]	.42**	-.38**
Neurological deficits[d]		
SSS score without language item	-.38**	.31**
Visual field deficit	.16	-.05
Old brain infarcts	-.06	-.11

Test statistics: The bivariate *Rho* was computed between the total outcome score and baseline scores or between the total outcome score and the two-level dichotomized baseline score. mRS, modified Rankin Scale; FAI, Frenchay Activities Index; SSS, Scandinavian Stroke Scale; [a]Visuospatial inattention was coded into three ordinal levels; Lateralized visual inattention (1), Visual inattention (2), No visual inattention (3). Language impairment was coded into three ordinal levels; Severe language impairment (1), Mild language impairment (2), No language impairment (3). [b]One patient who did not perform the SCT could not be retrospectively classified for visuospatial inattention at baseline and was not assessed on the mRS and FAI at follow-up. [c]Patients who did not perform the SCT or SSS at baseline were retrospectively classified for the presence of VSI and LI. [d]Four patients did not have a total score in SSS. ***P* < .01 (2-tailed).

Table 7 summarizes the results from the multivariable regression analysis of mRS and FAI and shows the statistically significant predictors in each model. The analyses identified visuospatial inattention and SSS as independent predictors both for the mRS score and the level of activity according to FAI.

Table 7. Predictors of mRS and FAI at 7 years after index stroke.

	Standardized coefficients		Importance	*df*	*F*	*P*
	B	SE				
Outcome: modified Rankin Scale (mRS)						
Visuospatial inattention	-.692	.201	.858	2	11.903	**< .001**
SSS score[a]	-.224	.106	.188	2	4.457	**.014**
Outcome: Frenchay Activities Index (FAI)						
Visuospatial inattention	.700	.242	.968	2	8.375	**< .001**
SSS score[a]	.228	.123	.215	3	3.430	**.029**

The model for mRS: $\boldsymbol{R^2}$ = .558, **F** = 14.354, **df** = 8, $\boldsymbol{p} < .001$, **Adjusted** $\boldsymbol{R^2}$ = .519
The model for FAI: $\boldsymbol{R^2}$ = .390, **F** = 7.276, **df** = 8, $\boldsymbol{p} < .001$, **Adjusted** $\boldsymbol{R^2}$ = .336
Multiple regression with optimal scaling (CATREG). The Importance indicates the contribution of each predictor to the model (in percentage). Visuospatial inattention was coded into three nominal levels; Lateralized visual inattention, Non-lateralized visual inattention, No visual inattention. Patients who did not perform the SCT or SSS at baseline were retrospectively classified for the presence of VSI and LI. [a]Total score without language item. Patients with missing values were excluded.

Additional analyses of outcomes

The presence and possible overlap between visuospatial inattention (VSI) and language impairment (LI) was analyzed. The participants with signs of LI and VSI were divided into two main groups. Patients exhibiting signs of both VSI (lateralized visual inattention or non-lateralized visual inattention) and language impairment (mild or severe impairment) were combined into one group (Combined symptoms, *n* = 13). The participants with non-combined symptoms constituted the other group (*n* = 34). The latter group consisted of those with either signs of mild language impairment (MLI, *n* = 18), severe language impairment (SLI, n = 6), non-lateralized visual inattention (NLVI, *n* = 8), or lateralized visual inattention (LVI, *n* = 2).

A statistically significant difference was observed between the non-combined group and the group with combined symptoms in relation to outcome of mRS (Mann-Whitney *U* test: Z = -3.02, $p < .003$) and FAI (Z = 2.79, $p < .004$).

Retrospective classification of VSI and LI

We further investigated the proportion of retrospectively classified individuals in the combined symptom group and the non-combined group. In the group with combined VSI and LI the proportion of retrospectively classified individuals was significantly higher compared to the non-combined group (53.8 % and 8.8 % respectively, $\chi2$ = 11.38, p = .002).

In the group with combined symptoms (*n* = 13), seven were retrospectively classified as having lateralized visual inattention (LVI) of which all except one had severe language impairment (SLI). This subgroup (SLI + retroLVI, *n* = 6) had the highest level of dependency on the mRS compared to the other participants in the combined group (*n* = 7, Mann-Whitney *U* test: Z = -2.53, p = .022) and compared to the non-combined groups SLI (Z

= -2.76, *p* = .009), MLI (Z = -3.54, *p* < .001), and the NLVI group (Z = -2.01, *p* = .050). A comparison with the LVI group was not possible due to only two cases in this group. A similar pattern was observed for outcome in FAI with the lowest scores for activity level for the subgroup SLI + retroLVI (Mean 14.5). However, a significant difference was only observed for the non-combined group MLI (Z = -3.24, *p* = .001).

In this study, twelve patients had missing data on the test of VSI and six of these participants had SLI and were unable to carry out the test. For these six, all were identified as having LVI at the retrospective evaluation. Thus, participants with LVI among those with SLI would have been overlooked if no retrospective classification had been made. Patients with the combination of SLI and retrospectively classified LVI had the most inferior long-term functional outcome.

Finally, we investigated whether the inclusion of retrospectively classified participants had an influence on the correlations between early VSI and the long-term outcome scores (earlier described in Table 6). We found that these correlations were lower when the retrospectively classified individuals were not included (Spearman's *rho* -.33, *p* = .001 between VSI and mRS and .31, *p* = .002 between VSI and FAI) compared to when they were included (Spearman's *rho* -.50, *p* < .001 between VSI and mRS and .45, *p* < .001 between VSI and FAI).

Study III

In study III, 188 participants were included at the 7-year follow-up. At the follow-up, 12 individuals were classified as lateralized inattention based on cancellation tests, 15 according to the neglect item of NIHSS, and 22 based on any of the cancellation tests or the neglect item of NIHSS. Table 8 shows the included participants classified as no lateralized inattention (*n* = 166) or lateralized inattention (*n* = 22).

Two-group analyses (Table 8) revealed that presence of lateralized inattention at follow-up was significantly associated with baseline inferior scores on total omissions, omission asymmetry, processing speed, stroke severity (SSS), and total anterior circulation infarcts.

Table 8. Relation between baseline assessments and presence of lateralized inattention at 7 years after index stroke.

	7-year follow-up assessment		
	No lateralized inattention	Lateralized inattention	Two-group comparisons
	n = 166	*n* = 22	*P*
Baseline assessment			
Demographics			
Age (years)	56 (12.0)	54.0 (11.8)	0.927
Females	61 (36.7)	8 (36.4)	1.000
Education ≤9 years[a]	51 (30.7)	6 (27.3)	0.810
Cancellation tests (SCT & LCT)			
Total omissions	2.5 (4.1)	10.1 (27.1)	**0.002**
Omission asymmetry	2.5 (5.0)	6.5 (11.0)	**0.003**
Processing speed			
SCT (30 sec)	49.0 (17.2)	27.0 (18.0)	**< 0.001**
Clinical characteristics			
SSS score	54 (8.5)	42.0 (34.0)	**0.003**
Visual field deficit	15 (9.0)	4 (18.2)	0.248
CT/MRI results			
Localization of index stroke lesion			
Supratentorial[b]	130 (79.8)	18 (81.8)	1.000
Right hemisphere[c]	55 (42.3)	11 (61.1)	0.205
Old brain infarcts	41 (24.7)	3 (13.6)	0.298
The Oxford Project Stroke Classification			
Lacunar infarcts	57 (35.0)	6 (27.3)	0.633
Total anterior circulation infarcts	11 (6.7)	10 (45.5)	**< 0.001**
Partial anterior circulation infarcts	43 (26.4)	2 (9.1)	0.110
Posterior circulation infarcts	52 (31.9)	4 (18.2)	0.225
Not possible to classify	3 (1.8)	0	-
Cardiovascular risk factors (yes)			
Hypertension	91 (55.2)	13 (59.1)	0.821
Diabetes mellitus	27 (16.3)	6 (27.3)	0.232
Hyperlipidemia	119 (75.3)	17 (77.3)	1.000
Smoking	58 (35.2)	9 (40.9)	0.639

SCT, Star Cancellation Test; LCT, Letter Cancellation Test; SSS, Scandinavian Stroke Scale; CT, computed tomography; MRI, magnetic resonance imaging. [a]Data about education was collected at the 7-year follow-up. [b]Supratentorial lesions were compared with infratentorial lesions. Three patients had multiple lesions and were not included in this analysis. [c]Right hemisphere lesions were compared with left hemisphere lesions resulting in a total n = 130 (No lateralized inattention group) and n = 18 (Lateralized inattention group). Patients in the no lateralized inattention group with missing data: Cancellation tests (SCT & LCT), 10; SCT (30 sec), 12; SSS score, 5; hypertension, 1; hyperlipidemia, 8; smoking, 1. Patients in lateralized inattention group with missing data: Cancellation tests (SCT & LCT), 6; SCT (30 sec), 7; SSS score, 1. Data are given as median (interquartile range) or n (%). Bold values indicate $P \leq 0.05$.

The multivariable regression analysis (Table 9) identified inferior baseline performance on total omissions and processing speed in SCT (30 sec) as independent predictors for presence of lateralized inattention at follow-up.

Table 9. Multivariable regression analysis of predictors for presence of lateralized inattention at the 7-year follow-up

	Estimate	Std Error	Wald ChiSquare	P-value	Lower/Upper 95% CI
Presence of lateralized inattention at 7 years					
Age	-0.065	0.042	2.358	0.125	-0.147 / 0.018
Gender	0.679	0.771	0.775	0.379	-0,833 / 2.191
Total omissions	0.158	0.037	18.576	**< 0.001**	0.086 / 0.229
Processing speed	-0.056	0.021	7.057	**0.008**	-0.100 / -0.015
Localization of index stroke lesion	0.934	0.799	1.367	0.242	-0.632 / 2.500

The estimation method lasso was used and validation method used as selection criteria was AICc. Patients with missing data or recurrent stroke were not included. Bold values indicate $P \leq 0.05$.

Study IV

Patterns of change in processing speed

Figure 2A illustrates the pattern of change in PS across the follow-ups for the 148 included participants in study IV. We found a significant difference between the scores at the three time points. A significant improvement in PS was observed from baseline to 3 months (Wilcoxon test: $Z = -7.16$, $p < .001$) and a decline from 3 months to the 7-year follow-up ($Z = -9.92$, $p < .001$).

We observed that 32 % of the participants at baseline displayed a score below the cut-off level for impaired performance. At 3 months, 16 % showed impaired performance and at the 7-year follow-up 58 % of the participants displayed impairments in speed. In general, no improvement of impaired speed was found in the long-term.

By dividing all participants into three groups (slow, mid, and fast group) based on their baseline scores (Figure 2B) we investigated whether those with scores in the slow speed group still performed at the lowest level at 3 months and at 7 years post-stroke when compared to the other groups (mid and fast group), and if those with scores in the mid and fast group also maintained their relative position i.e. mid and fast across time. For PS at 3 months, all two-group comparisons (Mann-Whitney *U* test) between the three groups (slow, mid, and fast) were statistically significant (Z-scores between -3.31 to -6.88, *p*-values between < .001 to .001) demonstrating that the relative position was maintained between the groups at this stage. The same was true for the 7-year time point, with statistically significant two-group comparisons between the groups (Z-scores between -2.80 to -6.22, *p*-values between .004 to <. 001).

For the slow speed group, all scores were below the cut-off level for possible impaired performance at baseline and 88 % of the participants were still below this level at 7 years. For the mid speed group these numbers were 37 % at baseline and 74 % at 7 years. For the fast speed group none had impaired performance at baseline, however, 38 % of these participants exhibited impaired performance at the 7-year follow-up (Figure 2B).

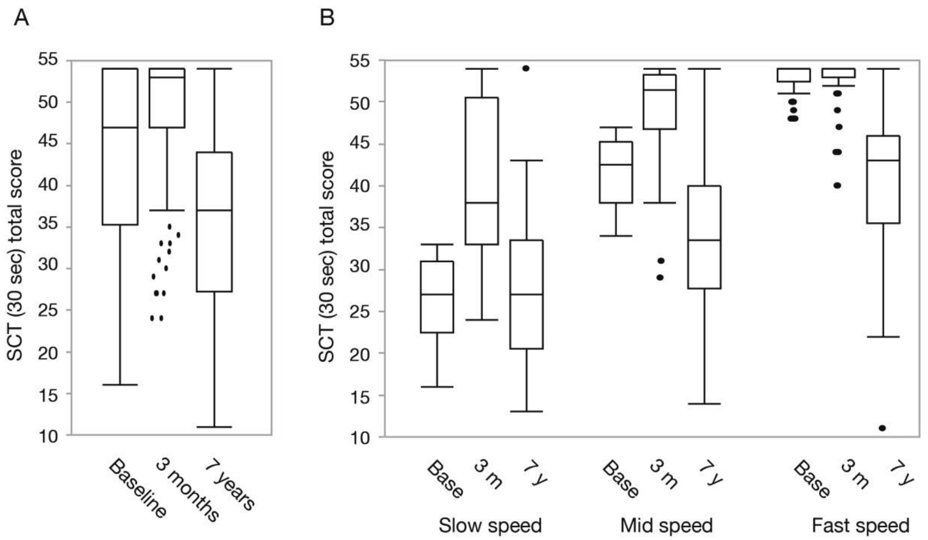

Figure 2. Overall pattern of change in PS across time. SCT (30 sec), Star Cancellation test with a time limit of 30 seconds. **(A)** Scores on SCT (30 sec) at baseline, 3 months, and at 7 years. **(B)** Scores on SCT (30 sec) for participants divided into three groups: ≤25 percentile (score 0-35, *slow speed*), <median (score 36-46, *mid speed*), ≥median (score 47-54, *fast speed*). Number of participants: slow speed group (n = 37), mid speed group (n = 32), fast speed group (n = 79).

Associations between processing speed, age, and outcomes at 7 years

The association between speed and age at baseline and at 7 years was significant at both these time points ($p < .001$). By dividing the participants into one group with PS scores ≤ median (*lower speed*) and another group with scores > median (*higher speed*) a remaining correlation was observed only for the higher speed group. This was observed both at baseline and at 7 years but was statistically significant only at the 7-year follow-up ($p < .010$).

Analyses of bivariate associations between PS and ratings on functional outcome at 7 years, showed that slower PS at all three time points was significantly associated with inferior outcome in mRS, FAI, and SIS (all *p*-values <.001) with the highest correlations observed at the 7-year follow-up (Spearman's *rho* .48 to .54, $p < .001$). At the age adjusted analyses of these correlations, slow speed was still significantly associated with worse outcomes ($p = .001$) at similar levels as the earlier unadjusted correlations. This was true for all three outcome measures both at baseline and at the 7-year follow-up.

Patterns of change in processing speed, neurological deficits, and inattention

For neurological deficits and inattention in conventional neglect tests, similar patterns of improvement in score were observed. A significant reduction in overall neurological deficits was observed from baseline to both the 3-month (Wilcoxon test: Z = -8.94, $p < .001$) and the 7-year follow-up (Z = -8.41, $p < .001$). For visual inattention a significant improvement in total number of cancellations was observed from baseline to both the 3-month and the 7-year follow-up and these observations were true for participants with lateralized as well as non-lateralized visual inattention (Z-scores between -2.56 and -3.41, *p*-values between .008 and < .001).

In contrast to these improvements for neurological deficits and visual inattention, there was a decline in PS scores from baseline to 7 years and from 3 months to 7 years (Z-scores between -2.48 and -8.48, *p*-values between .011 and < .001).

Discussion

Study I

The aim of study I was to investigate if a basic screening of visuospatial inattention (VSI) and language impairment (LI) at the early stage after stroke could provide prognostic information about long-term functional outcomes. It was found that early symptoms of VSI predicted unfavorable outcomes in terms of disability and frequency of performance in instrumental activities of daily living 7 years post-stroke. On the other hand, the early screening of LI did not provide any further prognostic information beyond the information provided by VSI and SSS.

Our findings support previous long-term studies with a one-year follow-up where both neglect and aphasia were included into the analyses (Appelros, et al., 2003; Giaquinto et al., 1999; Paolucci et al., 2000; Young et al., 2001). The current result adds information about the importance of neglect as an early predictor of functional outcome also several years after stroke. Further, our observations suggest that inclusion of a basic paper and pencil test of VSI at the post-acute stage can identify a group of patients at risk of unfavorable long-term outcomes where targeted rehabilitative interventions may be motivated.

Study II

The aim of study II was motivated by 1) the observations in study I that stroke laterality was not related to the outcome which indicated that VSI might provide information of long-term functional outcome following a left hemispheric stroke and 2) the findings in the literature that the incidence of neglect after a left hemisphere stroke may be biased as patients with severe aphasia often are excluded due to reduced comprehension. The aim was to investigate to what extent VSI is a predictor of long-term functional outcome for patients with a left hemispheric stroke, also including patients with severe language impairments.

Results from study II showed that presence of VSI was rather common after a left hemispheric stroke, observed in about one of five patients and it was the strongest independent predictor both for the level of disability (mRS) and for the frequency of performance in daily activities (FAI).

Interestingly, further investigations of the left hemisphere group demonstrated that the individuals with a combination of both VSI and LI were those with the most unfavorable long-term outcome concerning the level of disability and the frequency of performance in activities of daily living at the 7-year follow-up. Most of the patients with lateralized visual inattention (LVI) in this group also had severe language impairment (SLI) and it was found that without the extra retrospective classification of VSI several patients with LVI would have been overlooked among the patients with SLI. It was also found that these participants with a combination of SLI and a retrospectively classified LVI had the most inferior long-term outcome. The results demonstrate that an extra attempt to include patients with severe language impairments is important in this type of studies.

Our findings support the observations made in study I concerning the importance of investigating early symptoms of VSI for prediction of long-term functional outcome and especially so for patients with left hemispheric stroke. The observed influence of VSI on patients with LI in the same study is interesting since it is in line with the suggestion made by Murray (2002) that it is important to consider the possible impact that attentional impairments may have on individuals with language impairments.

Study II showed that by conducting a basic classification of presence of neglect at the acute phase especially for those with severe symptoms of aphasia after a left hemisphere stroke, important information about unfavorable long-term functional outcome could be obtained.

Study III

This study aimed to investigate long-term presence of lateralized inattention 7 years post-stroke and identify baseline predictors for presence of these symptoms. Study III was motivated by the lack of studies on unselected stroke cohorts that describe presence of lateralized inattention in the long-term perspective.

Results showed that about one out of ten participants had signs of lateralized inattention at 7 years. These findings are in line with observations made in other studies of unselected stroke patients that investigated presence of lateralized inattention at 4 years (Kotila., et al 1986) and 20 months post-stroke (Linden et al., 2005). We also found that inferior scores on total omissions in cancellation tests early after stroke were an important predictor for presence of lateralized inattention. This observation is in line with findings in earlier studies reporting that initial neglect severity (Karnath et al., 2011) and inferior initial scores on visuospatial attention (Ramsey et al., 2017) are associated with long-term presence of visuospatial neglect (Karnath et al., 2011) or inattention (Ramsey et al., 2017) at follow-up.

We also found that inferior performance in processing speed in a cancellation test was an important independent baseline predictor of long-term lateralized inattention. This finding is interesting since previous stroke studies have suggested that decreased speed appears to underlie cognitive dysfunction such as in visuoperceptual function (Su et al., 2015; Winkens et al., 2006).

This is the first time speed is recognized as a significant predictor of long-term lateralized inattention. These observations add to the existing literature suggesting a central role for processing speed for long-term cognitive outcomes after stroke and motivate further research in this area.

Study IV

This study describe the patterns of change in PS across three time points and it was motivated by reports that processing speed is an important component behind cognitive and functional outcome and the lack of knowledge in the stroke literature about long-term changes in processing speed.

About one third of all patients displayed impaired performance in speed at baseline and an improvement in scores from baseline to 3 months post-stroke. The observation of an early improvement in our study is in line with reports that a relatively fast recovery of higher cognitive functions often is observed during the initial months after stroke injury (Marchi, Ptak, Di Pietro, Schnider, & Guggisberg, 2017; Ramsey et al., 2017). A different pattern of PS scores emerged from the 3-month to the 7-year follow-up with the majority of participants displaying a decline in speed. The scores at this late time point was often at a similar or lower level than at the starting point at baseline and only few participants had improvements in speed from 3 months to 7 years. These results show that it is important to study the change in PS over a longer period since the initial improvement was altered to a decline in performance in the long-term.

Participants with the slowest speed at baseline still performed at the lowest level at both the 3-month and the 7-year follow-ups and it was found that the relative position was maintained during the two follow-ups for all levels of speed.

The patterns of change for PS, neurological deficits, and for visual inattention from baseline to 3 months were similar and showed improvements in scores. However, an apparent difference emerged between 3 months and 7 years with improvements or no change for neurological deficits and inattention but with a clear-cut decline in performance of PS. A decline in PS has been indicated in other studies during the six first months (Rasquin et al., 2002) up to six years (Comijs et al., 2009) after stroke. Our results confirm these observations of late decline in speed.

We also showed that age was related with the PS scores but did not explain the correlation with long-term outcomes and it did not explain the scores of PS for those with the slowest speed. Finally we demonstrated that there is an ecological value for investigating PS in the stroke patients as slow speed was related to inferior outcomes at the 7-year follow-up.

These findings clearly indicate the importance of investigations about PS following stroke, especially in longitudinally and long-term studies and exploring associations with functional outcomes and other potential correlates.

Summary of main findings

The main findings of studies I-II were that VSI was commonly observed at the acute phase not only after a right hemisphere stroke but also following a left hemisphere stroke. VSI after a left hemisphere stroke was actually the strongest independent predictor of unfavorable functional outcomes. A combination of VSI and language impairments (LI) was rather common at the acute phase after a left hemispheric stroke and individuals with this combination exhibited the most unfavorable long-term outcomes, especially so for those with a combination of severe language impairment (SLI) and retrospectively classified lateralized visual inattention (LVI).

Our findings demonstrated the importance of conducting an identification of visuospatial inattention at the early stage for individuals with severe impairments in language following a left hemispheric stroke, that is, for patients who often cannot complete a basic screening of VSI. Without additional evaluation procedures patients with LVI will be overlooked among patients with SLI.

Studies III-IV (together with the findings from studies I-II) emphasize that rather basic assessments of PS and VSI early after stroke can provide important prognostic information in terms of prediction of persisting signs of lateralized inattention and unfavorable functional outcome in the long-term, 7 years post-stroke. Initial improvements during the first three months were a dominating observation for PS, overall neurological deficits as well as for visual inattention in conventional neglect tests (study IV). However, from 3 months to 7 years a decline was demonstrated for PS while continued improvement or unchanged scores were observed in both neurological deficits and inattention. Thus, long-term studies are important in order to identify decline in speed.

GENERAL DISCUSSION

Neglect after a left hemispheric stroke

In the present studies lateralized visual inattention was not only observed after damage to the right hemisphere but also after left sided damage. This finding is in line with earlier studies that have described neglect following left hemisphere stroke even if the typical observation is neglect after a right hemispheric stroke. In a review by Bowen et al. (1999) of 17 stroke studies a median prevalence rate of 21% of neglect was reported after left brain damage and in a study by Beis et al. (2004) of 78 patients a prevalence of neglect in drawing and cancellation tasks of 13% was reported. When neglect is observed after a left hemispheric stroke it is often seen together with aphasia and the location of the brain damage is similar to the critical regions of the right hemisphere known to be associated with neglect and it has been suggested that attention and language functions may be represented in overlapping areas in the left hemisphere (Beume et al., 2017; Suchan & Karnath, 2011). Brain systems for visuospatial attention are in general regarded as lateralized to the right hemisphere but the above observations indicate that some types of spatial attention are also directed from systems in the left hemisphere. For a further discussion see for example Suchan and Karnath (2011) or Corbetta and Shulman (2011).

Left hemispheric stroke, neglect, aphasia, and long-term functional outcome

For the left hemispheric group, it was found that the combination of impairments in attention and language resulted in the most severe limitations in terms of dependency and participation in daily activities. An interesting question is how these observations can be understood in terms of brain recovery. Two aspects will be discussed in relation to recovery – a domain-general multifunctional perspective and a multiple network perspective. A domain-general multifunctional perspective on recovery is a new approach within the aphasia research arguing that the understanding of the severity and evolution of aphasia requires that the effect of other cognitive functions is included in the examination (Cahana-Amitay & Albert, 2015; Hodgson, Benattayallah, & Hodgson, 2014). The finding in our study that the combination of both severe language impairments and lateralized visual inattention resulted in the most severe functional outcome compared with those participants with only one of these symptoms is in line with this proposal. Another present approach is to understand recovery from a multiple network perspective. Several studies have demonstrated that the understanding of different cognitive functions such as attention and language is facilitated by the increased knowledge about the different functional and structural networks of the brain (Baldassarre, Ramsey, Siegel, Shulman, & Corbetta, 2016a; Geranmayeh, Leech, & Wise 2016). Different manifestations of neglect and aphasia can probably be understood better from a brain network perspective. Specific networks and white matter tracts have been connected to both language/aphasia and to attention/neglect. For example, the posterior arcuate fasciculus has been connected with language and superior longitudinal fasciculus II and III have been connected to visuospatial attention (Ramsey et al., 2017). Different changes in the pattern of activation across these networks (both intrahemispheric and interhemispheric) after a brain lesion, and between these networks and other networks, have been connected with a change in the symptoms and the recovery at different time scales (Baldassarre, et al., 2016b; Geranmayeh et al., 2016; Ramsey et al., 2017). The two approaches described above open for further research regarding neglect, aphasia and long-term functional outcome. The network and white matter approach open for questions about the possible correlates between deep white matter damage and the pattern of recovery. The domain-general multifunctional perspective opens for further questions about the possible interaction between impairments of domain-specific functions and domain-general functions and the interaction with white matter damage.

The cut-off levels for the SCT

In studies I-II and IV the cut-off score of ≤ 52 was based on a control group (*n* = 25) aged below 70 years from a previous study (Samuelsson et al., 1995) with a similar age range as our present stroke sample. This cut-off score was set at one point below that of the lowest score achieved by the controls. Our cut-off level is one point above the original cut-off score for the SCT (score ≤ 51) (Halligan et al., 1991; Wilson et al., 1987). This cut-off was set at one point below the lowest score achieved by 50 control subjects aged between 22-82 years. It is probable that we achieved the somewhat higher cut-off compared to Halligan et al. (1991) and Wilson et al. (1987) because our control subjects were within a younger age range. A study by Lindell et al. (2007) achieved the same cut-off as in our studies by using the same cut-off criterion (one point below the lowest score) on a control group (*n* = 31) of similar age range (25-73 years). Lower cut-off levels for the SCT (such as ≤ 48) has been reported among elderly subjects (Marshall & Halligan, 1989) and Stone, Halligan, Wilson, Greenwood, and Marshall (1991) recommended a cut-off < 39 based on a control group of 47 subjects with an upper age range of 93 years. Taken together, lower cut-off levels for the SCT can be expected with older controls and it is important to emphasize the upper age range of the matched control group when the cut-off criterion is set at one point below that of the lowest score achieved by the controls.

The criterion for classification of lateralized visual inattention (studies I-II and IV) and lateralized inattention (study III) was omission of at least three more targets at one half of the test sheet. This type of criterion can appear somewhat ambiguous, especially in cases where patients show omissions on both sides of the test sheet although fulfilling the criterion for a lateralized inattention. The rationale behind our choice was based on previous studies by our research group of neglect following stroke. These indicate that an increased number of omissions is highly correlated (unpublished data) with the lateral asymmetry of the location of the omissions measured with percentage score of asymmetry (Spearman's *rho* =

.72, $n = 54$) or with the Center of Cancellation (CoC) score of asymmetry ($rho = .70$, $n = 55$). Thus, more omissions were associated with more severe lateralized inattention while few omissions were associated with less obvious asymmetry. Consequently, it seemed most important to state the lowest level for a lateral difference for those cases with few omissions – the cut-off level for the smallest difference that could be justified as a lateral difference. With a difference of three more targets at one side as the cut-off the lowest number of omissions and the corresponding smallest difference are: 3 omissions with a difference 0:3; 4 omissions with a difference 0:4; 5 omissions with a difference 1:4; and 6 omissions with a difference 1:5. We regarded this level (three more targets at one side) as the lowest possible cut-off with a reasonable degree of lateral difference in the location of the omissions for those with few omissions.

Sensitivity and specificity of cancellation tests

Due to the well-known heterogeneity of the neglect syndrome several studies (Halligan, Marshall, & Wade, 1989; Lindell et al., 2007) have proposed that more than one subtest from a conventional test battery of neglect, such as the BIT (Wilson et al., 1987), should be used for a more efficient detection of neglect early after stroke (Halligan et al., 1989; Lindell et al., 2007). It has also been proposed that a combination of two subtests e.g. SCT and LCT can result in high sensitivity and specificity (Jehkonen et al., 1998).

In studies I-II the reason behind the choice to select one single test (the SCT) for the assessment of visuospatial inattention was two-folded. Firstly, it can be an advantage to use a rather basic measure as it confines the number of excluded patients due to inability to complete the test. Secondly, the SCT has previously been found to be a sensitive single measure at the acute phase following stroke (Halligan et al., 1989; Halligan, Wilson, & Cockburn, 1990; Jehkonen et al., 1998; Lindell et al., 2007) and easy to perform and to score in a clinical setting (Azouvi et al., 2002). Other single tests that have shown to be sensitive for detecting neglect after acute stroke are for example Posner's spatial cueing task of attention (Rengachary et al., 2009), Letter cancellation (Ferber & Karnath, 2001; Halligan et al., 1990; Jehkonen et al., 1998), and Bells test (Azouvi et al., 2002; Ferber & Karnath, 2001).

It has been demonstrated that the SCT is less sensitive to detect signs of neglect in the longer perspective after stroke (Rengachary et al., 2009). At the 7-year follow-up described in study III the assessment of lateralized inattention was not based on the SCT only but also on two additional measures (the LCT and the extinction/neglect item of the NIHSS). This approach may have resulted in a more heterogeneous group but we believe the combination of these measures increased the sensitivity for detecting signs of lateralized inattention at this late stage post-stroke.

The SSS language subscale

The classification of acute aphasic symptoms with the use of SSS subscale into mild and severe aphasia may have been misleading since the two most severe levels in SSS are based on the production of language and the length of sentences in the speech while the mild level in SSS was based on limited vocabulary or incoherent speech. This could mean that the severe level may be biased against a motor/Broca type of aphasia while the mild level may have included both sensory/Wernicke type (incoherent speech) and motor/Broca type (limited vocabulary). Thus, it might mean that the scale is better described as a nominal scale (different types of language impairments) than as an ordinal scale (more or less severe symptoms). However, in the first study in the current thesis no difference in the outcome was observed for the use of nominal or ordinal scale for language impairment but for study II the nominal scale gave a better fit to the outcome variable and was used in the multivariable analysis. The latter finding might indicate that the nominal level was more adequate.

It should be mentioned that a thorough examination of language impairment carried out by a speech pathologist is the golden standard and that the use of the SSS subscale is a rather simple method for identification of language impairments although the validation of language impairments by the use of medical records offered valuable additional information. It is unlikely that patients with marked impairments were misidentified but individual cases with subtle symptoms may have been overlooked, neither we cannot fully exclude the possibility of false positives.

Lateralized inattention in the late stage after stroke

Lateralized inattention is a typical sign of the neglect phenomenon and is considered as most pronounced during the first three months after stroke (Cassidy et al., 1998; Nijboer et al., 2013) and about one third of patients with neglect still show these symptoms at three months or more post-stroke (Cassidy et al. 1998; Karnath et al., 2011). There are few long-term studies of unselected stroke samples with follow-ups beyond the first year (Kotila et al., 1986; Linden et al., 2005) with a reported neglect frequency of 10-15 %. These observations are in line with our findings of a similar frequency observed up to 7 years post-stroke. We found an association between early overall omissions in cancellation tests and lateralized inattention at 7 years. These observations are supported by studies reporting that initial neglect severity (Karnath et al., 2011) and inferior initial scores on visuospatial attention (Ramsey et al., 2017) are associated with long-term presence of visuospatial neglect (Karnath et al., 2011) and inattention at follow-up (Ramsey et al., 2017). Notably, in the long-term perspective, more subtle symptoms of lateralized inattention may be detected with more demanding tasks (Bonato, 2015; Rengachary et al., 2009).

In study III, it is important to consider the potential influence of old brain infarcts on cognition. However, our reported results did not suggest that old brain infarcts were associated with presence of lateralized inattention at 7 years post-stroke since the majority of individuals (41 of 44) with old brain infarcts were classified with no lateralized inattention at follow-up. Further, in study I, we showed that old brain infarcts were not a significant baseline predictor for unfavorable functional outcomes regarding the level of disability (mRS) and the frequency of performance in activities of daily living (FAI) at 7 years.

Processing speed and lateralized inattention after stroke

The results in this thesis showed that processing speed was a significant independent predictor for lateralized inattention at 7 years, that is, low speed at the early stage after stroke was related to presence of lateralized inattention 7 years later. At an additional analysis (not reported in this thesis) it was observed that those with the lowest level of visual attention in conventional neglect tests (SCT and LCT) at 7 years had the lowest (most impaired) speed, both for the speed scores at baseline and at 7 years. This indicates that although there is a clear improvement in the performance in conventional cancellation tests at 7 years post-stroke, there is still a group of patients with lateralized and/or non-lateralized visual inattention at this late stage and this group has low speed at the early stage and probably also persistent low speed at 7 years. One may ask why slow speed at the acute stage (and probably also at 7 years) is connected to signs of VSI 7 years after the stroke? This study did not investigate possible mechanisms behind this relationship but earlier studies have suggested possible connections between lateralized inattention and slow performance in tests of PS (i.e. in tests with a time limit or timed tests). It has been suggested that patients with neglect exhibit both lateralized and non-lateralized behavioral impairments (Corbetta & Shulman, 2011; Karnath, 1988). One example of a non-lateralized component is the intensity aspects of attention such as lowered alertness/arousal and impaired aspects of sustained attention (Gerritsen, Berg, Deelman, Visser-Keizer, & Meyboom-de Jong, 2003; Rengachary et al., 2011; Robertson, 2001; Smania et al., 1998). Impairments of alertness/sustained attention for patients with neglect have been demonstrated in several studies in terms of slow and inconsistent reaction times (Anderson, Mennemeier, & Chatterjee, 2000; Làdavas, 1987; Posner & Rafal, 1987; Robertson, 2001; Samuelsson et al., 1998) and in other ways too (George, Mercer, Walker, & Manly, 2008). Robertson et al. (1993) did suggest that the recovery of neglect is influenced by the level of deficits in sustained attention and Robertson, Tegner, Tham, Lo, and Nimmo-Smith, 1995 showed that an induced improvement of alertness resulted in improvements in lateralized inattention in a group of individuals with neglect. Samuelsson et al. (1998) described a connection between persisting neglect at 6 months and slow speed in a test of simple reaction time. Furthermore, slow speed in tasks that include perceptual processing has been described as a central finding for individuals with neglect (Corbetta & Shulman, 2011), in simple visual tasks (Bartolomeo, 1997; Kaizer, Korner-Bitensky, Mayo, Becker, & Coopersmith, 1988; Làdavas, Petronio, & Umiltà, 1990; Smania et al., 1998), in visual search (Manly et al., 2009), and in more complex visual tasks (Gerritsen et al., 2003; Làdavas et al., 1990; Rengachary et al., 2011). Thus, the intensity aspect of attention (alertness/sustained attention) may represent a possible common mechanism (among others) behind PS and lateralized inattention. However, most of the research referred to above concerns observations after right hemisphere damage and less is known about the connection between speed and lateralized inattention for patients with left hemispheric stroke. There is also a gap of knowledge in the longer perspective about the possible importance of these non-lateralized components for the relation between PS and lateralized inattention.

Change in processing speed after stroke

It is interesting that inferior performance in speed tests typically has been observed in connection with different brain pathologies that result in white matter damage such as multiple sclerosis (Costa et al., 2017; Diamond et al., 2008), traumatic brain injuries (Felmingham, Baguley, & Green, 2004; Willmott et al., 2009), dementia (Wallin et al., 2016), and gliomas (Ek, Kristoffersen, & Vestberg, 2018). It is thus possible that tests of processing speed are specifically sensitive to the efficiency of the connections and communication within the brain. If this is true, the low speed at the acute stage following stroke may represent a behavioral sign of an acute disruption of structural and/or functional communication within and between the networks of the brain. A widely distributed abnormality in the functional communication has been described early after stroke in recent studies (Grefkes & Fink, 2011; Umarova et al., 2017). The recovery of the speed scores during the initial months may reflect the capacity of the brain to restore more normal patterns of communication (Ramsey et al., 2017). However, mechanisms behind recovery after brain lesions are complex and disrupted communication is of course only one among many possible components that may affect recovery.

In the long-term the speed performance declined and several subjects showed impaired performance in speed. One important component behind the decline may be age-related changes in white matter that can result in lowered speed performance (de Groot et al., 2000; Ferro & Madureira, 2002). Our findings indicate that the association with age was most obvious for those with relatively fast speed performance at the acute phase and thus other components may be more important for those with low speed at the early stage. It is possible that the long-term performance for the participants with low speed initially was affected more by long-term consequences related to the acute lesion.

Whatever the mechanisms may be behind the observed patterns, the results indicate that it can be of value to measure processing speed following stroke because it is sensitive to changes in brain functions and it is related to long-term functional outcome both as an early predictor and as a late correlate.

There are several important questions for future studies of processing speed after stroke. The connection between white matter changes and processing speed is of special interest and the relation with overall cognitive capacity is also interesting. A high number of patients with cognitive impairments late after stroke has been reported (Mchutchison et al., 2019; Redfors et al., 2014) and impaired PS with decline in the long-term was reported by us in study IV and by Comijs et al. (2009). These observations motivate further studies of the relation between decreasing speed, cognitive impairment and measures of white matter lesions and hyperintensities at the late stage and longitudinally. The possible influence of depression on PS is also of great significance. Another vital question is to what extent the level of visual field- and motor deficits influences the speed in visual speed tests. We have demonstrated (study IV) a significant correlation at the late stage between processing speed and functional outcome and one essential question is to what extent processing speed is related to functional outcome in a multivariable analysis including several other potential correlates.

Ethical considerations

The Regional Ethics Review Board at the University of Gothenburg approved these studies. Written informed consent was obtained from all participants. For those who were unable to communicate, consent was obtained from their next of kin. It is possible that the cognitive tests and questionnaires performed at the different visits can be perceived as tedious and it can be uncomfortable to perform these tests. These possibilities have been discussed within the group and those conducting the investigation have practiced on addressing these kinds of problems. The participants may become aware of possible inferior results during the investigation and may feel frustrated. However, for most of the participants it is instead a positive confirmation of problems they have experienced but not fully understood. Also, many participants and controls appreciate to participate in an important study and to contribute with essential information. Feedback of cognitive results is given when participants so wishes. All participants received early information about the study and that participation is voluntary and may be discontinued at any time, without reason being given.

Limitations

A limitation of the present studies was the use of rather basic assessments of VSI and LI after stroke. They do not differentiate between subtypes of neglect and aphasia and probably do not detect more subtle signs. It is likely that the frequency of long-term signs of lateralized inattention in this thesis is underestimated due to these basic measures. The use of one basic measure for the assessment of PS is another limitation. On the other hand, the use of rather basic assessments can also be an advantage since it confines the number of excluded patients due to inability to complete the tests.

It is likely that the behavioral signs of lateralized inattention following neglect at the early stage post-stroke are rather distinct and easy to detect for experienced staff at a stroke unit. Non-lateralized inattention on the other hand is commonly described in other terms such as lowered wakefulness or confusion. Consequently, the description of the latter phenomenon may be less clear why it is probable that non-lateralized inattention has been underestimated by the retrospective classification from the medical records used in this study.

Early aphasic symptoms may be related to more language specific aspects of functional outcome. It is therefore important to recognize the possible limitation of the types of outcome measures used in the present studies. The measures used were focused on different types of ADL, including basic as well as complex/social aspects. Other aspects of outcome that may be relevant for patients with language impairments were not investigated, such as outcomes in terms of functional communication skills, emotional distress, and quality of life. It is possible that the importance of aphasic symptoms could have been more pronounced with these types of measures. Further long-term studies, preferably with more comprehensive assessments of aphasia and more detailed outcome metrics are needed.

Several neuropsychological functions that could have influenced the results were not included in the current studies. Examples of such functions are general cognitive level, memory, and executive functions. We include such functions in our current research on cognition and stroke. Other factors that may influence long-term outcome in young patients with stroke, such as epileptic seizures were not included. Presence of depression at the baseline may also have influenced the long-term outcome but a reliable assessment of depression at the acute phase is difficult to obtain due to the acute symptoms and the emotional turmoil often experienced at this phase. These studies did not include information about the presence and length of a possible rehabilitation period, a component that might influence the long-term outcome.

The interpretations about impaired performance in PS (study IV) must be done with caution as the control group was rather small and scores were only collected from a single assessment and not at three time points as for the participants with stroke. At the two first assessments of speed following stroke, an obvious roof effect was observed for scores at the three-month follow-up. This probably resulted in inflated number of patients with no or mild improvements in scores at three months. A further limitation is the large time interval between assessments made at three months and seven years which made it difficult to establish when the decline in PS occurred.

Finally, the representativeness of the results in these studies is restricted to ischemic stroke patients <70 years at index stroke. The studies focused on a cohort of relatively young stroke survivors. The rationale for this focus was that increased knowledge of long-term outcomes in this group of individuals is crucial, as they have a long life expectancy and may live many years with stroke-related consequences during a period normally devoted to an active life. The restriction in age did also facilitate more reliable analyses due to less confounding influence of severe comorbidities and diffuse and multi-localized lesions that are more common in an elderly stroke population.

Conclusion and clinical implications

It was demonstrated that basic assessments of PS and VSI early after stroke can provide important prognostic information in terms of prediction of persisting signs of lateralized inattention and unfavorable functional outcome in the long-term, 7 years post-stroke. For patients with left hemispheric stroke, impairment in VSI was the most important correlate of long-term functional outcome and the combination of impairments in attention and language resulted in the most severe limitations in terms of dependency and participation in daily activities. A clinical implication is that it is important to examine the presence and absence of

VSI in patients with language impairments and especially in patients with severe impairments. This is important in order to obtain a nonbiased prevalence of neglect following left hemisphere damage and in order to obtain prognostic information about long-term outcome that hopefully can guide future rehabilitation. However, the investigation of patients with severe language impairment is complicated due to impaired comprehension and difficulties to complete the tests. Possible solutions might be to also include very simple tests that most of the patients with these severe impairments can complete or to use standardized rating scales that are based on clinical observations. Patients with severe language impairment and severe illness and therefore not possible to investigate can be classified retrospectively from the reports in the medical records. Elevated awareness in the clinical setting of possible acute impairments of visuospatial attention in combination with language impairments after left hemispheric stroke can hopefully facilitate the identification of important clinical baseline predictors of long-term functional outcome. Another clinical implication of our studies is that it is important to study change in PS over a longer period since the initial improvement in speed is followed by a decline in the long-term and the strongest associations with the outcomes is found at 7 years.

REFERENCES

Adair, J. C., & Barrett, A. M. (2008). Spatial neglect: Clinical and neuroscience review. *Annals of the New York Academy of Sciences, 1142,* 21-43. doi:10.1196/annals.1444.008

Ali, M., Lyden, P., Brady, M., and On Behalf of the VISTA Collaboration. (2013). Aphasia and dysarthria in acute stroke: Recovery and functional outcome. *International Journal of Stroke, 10,* 400-406.

Anderson, B., Mennemeier, M., & Chatterjee, A. (2000). Variability not ability: Another basis for performance decrements in neglect. *Neuropsychologia, 38,* 785–796.

Appelros, P., Karlsson, G. M., Seiger, A., & Nydevik, I. (2002). Neglect and anosognosia after first-ever stroke: incidence and relationship to disability. *Journal of Rehabilitation Medicine, 34,* 215-220.

Appelros, P., Karlsson, G. M., Seiger, A., & Nydevik, I. (2003). Prognosis for patients with neglect and anosognosia with special reference to cognitive impairment. *Journal of Rehabilitation Medicine, 35,* 254-258. doi:10.1080/16501970310012455

Azouvi, P., Samuel, C., Louis-Dreyfus, A., Bernati, T., Bartolomeo, P., Beis, J. M., …Rousseaux, M. French Collaborative Study Group on Assessment of Unilateral Neglect (GEREN/GRECO). (2002). Sensitivity of clinical and behavioural tests of spatial neglect after right hemisphere stroke. *Journal of Neurology, Neurosurgery, and Psychiatry, 73,* 160-166.

Baldassarre, A., Ramsey, L., Siegel, J., Shulman, G., & Corbetta, M. (2016a). Brain connectivity and neurological disorders after stroke. *Current Opinion in Neurology, 29*, 706-713.

Baldassarre, A., Ramsey, L., Rengachary, J., Zinn, K., Siegel, J., Metcalf, N., …Shulman, G. (2016b). Dissociated functional connectivity profiles for motor and attention deficits in acute right-hemisphere stroke. *Brain, 139*, 2024-2038.

Bamford, J., Sandercock, P., Dennis, M., Burn, J., & Warlow, C. (1991). Classification and natural history of clinically identifiable subtypes of cerebral infarction. *Lancet, 337,* 1521-1526.

Banks, J. L., & Marotta, C. A. (2007). Outcomes validity and reliability of the modified Rankin scale: Implications for stroke clinical trials: A literature review and synthesis. *Stroke, 38,* 1091-1096.

Barker-Collo, S., Feigin, V. L., Parag, V., Lawes, C. M., & Senior, H. (2010). Auckland stroke outcomes study. Part 2: Cognition and functional outcomes 5 years poststroke. *Neurology, 2,* 1608-1616.

Bartolomeo, P. (1997). The novelty effect in recovered hemineglect. *Cortex, 33,* 323–332.

Beis, J. M, Keller, C., Morin, N., Bartolomeo, P., Bernati, T., Chokron, S., …Azouvi, P. (2004). Right spatial neglect after left hemisphere stroke: Qualitative and quantitative study. *Neurology, 63*, 1600-1605.

Benson, F. D. (1993). Aphasia. In K. M. Heilman & E. Valeinstein (Eds.), *Clinical neuropsychology* (3rd ed, pp. 17-36). New York, NY: Oxford University Press.

Bersano, A., Burgio, F., Gattinoni, M., & Candelise, L. (2009). Aphasia burden to hospitalized acute stroke patients: Need for an early rehabilitation programme. *International Journal of Stroke, 4,* 443-447.

Beume, L-A., Martin, M., Kaller, C. P., Klöppel, S., Schmidt, C. S. M., …Umarova, R. M. (2017). Visual neglect after left-hemispheric lesions: A voxel-based lesion-symptom mapping study in 121 acute stroke patients. *Experimental Brain Research, 235,* 83-95.

Bickerton, W. L., Demeyere, N., Francis, D., Kumar, V., Remoundou, M., Balani, A., …Humphreys, G. W. (2015). The BCoS cognitive profile screen: Utility and predictive value for stroke. *Neuropsychology, 29,* 638-648. doi:10.1037/neu0000160

Bonato, M. (2015). Unveiling residual, spontaneous recovery from subtle hemispatial neglect three years after stroke. *Frontiers in Human Neuroscience*, *9,* 413.

Bonita, R., & Beaglehole, R. (1988). Recovery of motor function after stroke. *Stroke, 19*, 1497-1500.

Bowen, A., McKenna, K., & Tallis, R. C. (1999). Reasons for variability in the reported rate of occurrence of unilateral spatial neglect after stroke. *Stroke*, *30,* 1196-1202.

Boysen, G. (1992). The Scandinavian stroke scale. *Cerebrovascular Diseases, 2,* 239-240.

Brott, T., Adams, H. P. Jr., Olinger, C. P., Marler, J. R., Barsan, W. G., Biller, J., …Walker, M. (1989). Measurements of acute cerebral infarction: A clinical examination scale. *Stroke, 20,* 864-870.

Brust, J. C., Shafer, S. Q., Richter, R. W., & Bruun, B. (1976). Aphasia in acute stroke. *Stroke*, *7*, 167–174.

Buxbaum, L. J., Ferraro, M. K., Veramonti, T., Farne, A., Whyte, J., Làdavas, E., ...Coslett, H. B. (2004). Hemispatial neglect: Subtypes, neuroanatomy, and disability. *Neurology, 62,* 749-756. doi:10.1212/01.WNL.0000113730.73031.F4

Cahana-Amitay, D., & Albert, M. (2015). *Redefining recovery from aphasia*. Oxford, NY: Oxford University Press.

Cassidy, T., Bruce, D. W., Lewis, S., & Gray, C. S. (1999). The association of visual field deficits and visuo-spatial neglect in acute right-hemisphere stroke patients. *Age and Aging, 28,* 257-260.

Cassidy, T., Lewis, S., & Gray C. G. (1998). Recovery from visuospatial neglect in stroke patients. *Journal of Neurology, Neurosurgery, and Psychiatry, 64,* 555-557.

Cherney, L. R., & Halper, A. S. (2001). Unilateral visual neglect in right-hemisphere stroke: A longitudinal study. *Brain Injury, 7,* 585-592.

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences,* 2edn. Hillsdale, NJ: Lawrence Erlbaum Associates, Publishers.

Colombo, A., De Renzi, E., & Gentilini, M. (1982). The time course of visual hemi-inattention. *Archiv für Psychiatrie und Nervenkrankheiten*, *231,* 539-546.

Comijs, H. C., Kriegsman, D. M., Dik, M. G., Deeg, D. J., Jonker, C., & Stalman, W. A. (2009). Somatic chronic diseases and 6-year change in cognitive functioning among older persons. *Archives of Gerontology and Geriatrics, 48,* 191-196.

Corbetta, M., & Shulman, G. L. (2011). Spatial neglect and attention networks. *Annual Review of Neuroscience, 34,* 569-599. doi:10.1146/annurev-neuro-061010-113731

Costa, S., Genova, H., Deluca, J., & Chiaravalloti, N. (2017). Information processing speed in multiple sclerosis: Past, present, and future. *Multiple Sclerosis Journal, 23,* 772-789.

Dalemans, R. J. P., De Witte, L. P., Beurskens, A. J. H. M, Van den Heuvel, W. J. A., & Wade, D. T. (2010). An investigation into the social participation of stroke survivors with aphasia. *Disability and Rehabilitation, 32,* 1678-1685.

Damasio, A. R., & Damasio, H. (2000). Aphasia and the neural basis of language. In M. M. Mesulam (Ed.), *Principles of behavioral and cognitive neurology* (pp. 294-316). New York, NY: Oxford University Press.

de Groot, J. C., de Leeuw, F-E., Oudkerk, M., van Gijn, J., Hofman, A., Jolles, J., & Breteler, M. M. (2000). Cerebral white matter lesions and cognitive function: The Rotterdam Scan Study. *Annals of Neurology, 47,* 145-151.

Diamond, B. J., Johnson, S. K., Kaufman, M., & Graves, L. (2008). Relationships between information processing, depression, fatigue and cognition in multiple sclerosis. *Archives of Clinical Neuropsychology, 23,* 189-199.

Dickey, L., Kagan, A., Lindsay, M. P., Fang, J., Rowland, A., & Black, S. (2010). Incidence and profile of inpatient stroke-induced aphasia in Ontario, Canada. *Archives of Physical Medicine and Rehabilitation, 91,* 196-202. doi:10.1016/j.apmr.2009.09.020

D'Olhaberriague, L., Litvan, I., Mitsias, P., & Mansbach, H. H. (1996). A reappraisal of reliability and validity studies in stroke. *Stroke, 27*, 2331-2336.

Duncan, P. W., Wallace, D., Min Lai, S., Johnson, D., Embretson, S., & Jacobs Laster, L. (1999). The Stroke Impact Scale Version 2.0: Evaluation of rebiliabilty, validity, and sensitivity to change. *Stroke, 30,* 2131-2140.

Ek, L., Kristoffersen, Wiberg, M., & Vestberg, S. (2018). Decline in executive functions and speed in suspected low-grade gliomas: A 3-year follow-up of a clinical cohort. *Applied Neuropsychology: Adult, 25,* 376-384.

Engelter, S. T., Gostynski, M., Papa, S., Frei, M., Born, C., Ajdacic-Gross, V., …Lyrer, A. (2006). Epidemiology of aphasia attributable to first ischemic stroke: incidence, severity, fluency, etiology, and thrombolysis. *Stroke, 37,* 1379–1384. doi:10.1161/01.STR.0000221815.64093.8c

Farne, A., Buxbaum, L. J., Ferraro, M., Frassinetti, F., Whyte, J., Veramonti, T., …Làdavas, E. (2004). Patterns of spontaneous recovery of neglect and associated disorders in acute right brain-damaged patients. *Journal of Neurology, Neurosurgery, and Psychiatry, 75,* 1401-1410.

Felmingham, K., Baguley, I., & Green, A. (2004). Effects of diffuse axonal injury on speed of information processing following severe traumatic brain injury. *Neuropsychology, 18,* 564-571.

Feigin, V. L., Forouzanfar, M. H., Krishnamurthi, R., Mensah, G. A., Connor, M., Bennet, D. A., Moran, A. E., …Murray, C. (2010). Global and regional burden of stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet, 383,* 245-254. doi:10.1016/S0140-6736(13)61953-4

Ferber, S., & Karnath, H. O. (2001). How to assess spatial neglect—line bisection or cancellation tasks? *Journal of Clinical and Experimental Neuropsychology, 23,* 599-607.

Ferro, J. M., & Madureira, S. (2002). Age-related white matter changes and cognitive impairment. *Journal of the Neurological Sciences, 15,* 221-225.

Ferro, J. M., Mariano, G., & Madureira, S. (1999). Recovery from aphasia and neglect. *Cerebrovascular Diseases, 9,* 6-22.

Field A. (2005). *Discovering Statistics using SPSS,* 2edn. Thousand Oaks, CA, US: Sage Publications, Inc.

Flowers, H. L., Skoretz, S. A., Silver, F. L., Rochon, E., Fang, J., Flamand-Roze, C., & Martino, R. (2016). Poststroke aphasia frequency, recovery, and outcomes: A systematic review and meta-analysis. *Archives of Physical Medicine and Rehabilitation, 97,* 2188-2201.

Fullerton, K. J., McSherry, D., & Stout, R. W. (1986). Albert's test: a neglected test of perceptual neglect. *Lancet*, *1*, 430-432.

George, M., Mercer, J., Walker, R., & Manly, T. (2008). A demonstration of endogenous modulation of unilateral spatial neglect: The impact of apparent time-pressure on spatial bias. *Journal of the International Neuropsychological Society, 14,* 33-41.

Geranmayeh, F. J., Leech, R., & Wise, R. (2016). Network dysfunction predicts speech production after left hemisphere stroke. *Neurology, 86*, 1296-1305.

Gerritsen, M. J. J., Berg, I. J., Deelman, B. G., Visser-Keizer, A. C., & Meyboom-de Jong, B. (2003). Speed of information processing after unilateral stroke. *Journal of Clinical and Experimental Neuropsychology, 25,* 1–13.

Gialanella, B., & Ferlucci, C. (2010). Functional outcome after stroke in patients with aphasia and neglect: Assessment by the motor and cognitive functional independence measure instrument. *Cerebrovascular Diseases, 30,* 440-447. doi:10.1159/000317080

Gialanella, B. (2011). Aphasia assessment and functional outcome prediction in patients with aphasia after stroke. *Journal of Neurology, 258,* 343-349. doi: 10.1007/s00415 010 5868-x

Gialanella, B., Bertolinelli, M., Lissi, M., & Prometti, P. (2011). Predicting outcome after stroke. The role of aphasia. *Disability and Rehabilitation, 33,* 122-129.

Gialanella, B., Santoro, R., & Ferlucci, C. (2013). Predicting outcome after stroke: The role of basic activities of daily living predicting outcome after stroke. *European Journal of Physical and Rehabilitation Medicine, 49,* 629-637.

Giaquinto, S., Buzzelli, S., Di Francesco, L., Lottarini, A., Montenero, P., Ton in, P., & Nolfe, G. (1999). On the prognosis of outcome after stroke. *Acta Neurologica Scandinavica, 100,* 202-208. doi.10.1111/j.1600-0404.1999.tb00740.x

Gray, L. J., Ali, M., Lyden, P. D., & Bath, P. M. (2009). Interconversion of the National Institutes of Health Stroke Scale and Scandinavian Stroke Scale in acute stroke. *Journal of Stroke and Cerebrovascular Diseases, 18,* 466-468.

Green, J., Forster, A., & Young, L. (2001). A test-retest reliability study of the Barthel Index, Rivermead Mobility Index, the Nottingham extended Activities of Daily Living Scale and the Frenchay Activities Index in stroke patients. *Disability and Rehabilitation, 23,* 670-676.

Grefkes, C., & Fink, G. R. (2011). Reorganization of cerebral networks after stroke: New insights from neuroimaging with connectivity approaches. *Brain, 134,* 1264-1276.

Guariglia, C., & Pizzamiglio, L. (2007). The role of imagery in navigation: Neuropsychological evidence. In F. Mast & L. Jäncke (Eds.), *Spatial processing in navigation, imagery and perception* (pp. 17-28). New York, NY: Springer-Verlag.

Halligan, P. W., & Marshall, J. C. (1993). The history and clinical presentation of neglect. In I. H. Robertson & J. C. Marshall (Eds.), *Unilateral neglect: clinical and experimental studies* (pp. 3-26). Hove: Lawrence Erlbaum Associates.

Halligan, P. W., & Marshall, J. C. (1998). Neglect of awareness. *Consciousness and Cognition*, *7*, 356-380.

Halligan, P. W., Cockburn, J., & Wilson, B. A. (1991). The behavioural assessment of visual neglect. *Neuropsychological Rehabilitation, 1*, 5-32.

Halligan, P. W., Marshall, J. C., & Wade, D. T. (1989). Visuospatial neglect: Underlying factors and test sensitivity. *Lancet, 334,* 908-911.

Halligan, P. W., Wilson, B. A., & Cockburn, J. (1990). A short screening test for visual neglect in stroke patients. *International Disability Studies, 12,* 95-99.

Heilman, K. M., Watson, R. T., & Valenstein, E. (1993). Neglect and related disorders. In K. M. Heilman & E. Valenstein (Eds.), *Clinical Neuropsychology* (3rd ed, pp. 279-336). New York: Oxford University Press.

Heilman, K. M., Watson, R. T., & Valenstein, E. (1985). Neglect and related disorders. In K. M. Heilman & E. Valenstein (Eds.), *Clinical Neuropsychology* (2nd ed, pp. 243-293). New York: Oxford University Press.

Hier, D. B., Mondlock, J., & Caplan, L. R. (1983). Recovery of behavioral abnormalities after right hemisphere stroke, *Neurology, 33,* 345-350.

Hjaltason, H., Tegnér, R., Tham, K., Levander, M., & Ericson, K. (1996). Sustained attention and awareness of disability in chronic neglect. *Neuropsychologia, 34,* 1229-1233.

Ho, A. K., Manly, T., Nestor, P. J., Sahakian, B. J., Bak, T. H., Robbins, T. W., …Barker, R. A. (2003). A case of unilateral neglect in Huntington's disease. *Neurocase, 9,* 261-273. doi:10.1076/neur.9.3.261.15559

Hodgson, J. C., Benattayallah, A., & Hodgson, T. L. (2014). The role of the dominant versus the non-dominant hemisphere: An fMRI study of aphasia recovery following stroke. *Aphasiology,* 1-22.

Holbrook, M., & Skilbeck, C. E. (1983). An activities index for use with stroke patients. *Age, and Aging, 12,* 166-170.

Hreha, K., Mulry, C., Gross, M., Jedziniak, T., Gramas, N., Ohevshalom, L., Sheridan, A., …Barret, A. M. (2016). Assessing chronic stroke survivors with aphasia sheds light on prevalence of spatial neglect. *Topics in Stroke Rehabilitation, 20,* 1-8. doi:10.1080/10749357.2016.1196906

Ishiai, S., Koyama, Y., Seki, K., Orimo, S., Sodeyama, N., Ozawa, E., …Hiroki, M. (2000). Unilateral spatial neglect in AD: Significance of line bisection performance. *Neurology, 55,* 364–370.

Jansen, H. E., Schepers, V. P., Visser-Meily, J. M., & Post, M. W. (2012). Social activitiy one and three years post-stroke. *Journal of Rehabilitation Medicine, 44,* 47-50.

Jehkonen, M., Ahonen, J. P., Dastidar, P., Koivisto, A. M., Laippala, P., Vilkki, J. (1998). How to detect visual neglect in acute stroke. *Lancet, 7,* 727-728.

Jehkonen, M., Ahonen, J. P., Dastidar, P., Koivisto, A. M., Laippala, P., Vilkki, J., & Molnár, G. (2000). Visual neglect as a predictor of functional outcome one year after stroke. *Acta Neurologica Scandinavica, 101,* 195-201.

Jehkonen, M., Ahonen, J. P., Dastidar, P., Koivisto, A. M., Laippala, P., Vilkki, J., & Molnár, G. (2001). Predictors of discharge to home during the first year after right hemisphere stroke. *Acta Neurologica Scandinavica, 104,* 136-141.

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

Jehkonen, M., Laihosalo, M., Koivisto, A.-M., Dastidar, P., & Ahonen, J.-P. (2007). Fluctuation in spontaneous recovery of left visual neglect: A 1-year follow-up. *European Neurology, 58,* 210–214.

Jood, K., Ladenvall, C., Rosengren, A., Blomstrand, C., & Jern, C. (2005). Family history in ischemic stroke before 70 years of age: The Sahlgrenska Academy Study on Ischemic Stroke. *Stroke, 36*, 1383-1387.

Kail, R., & Salthouse, T. A. (1994). Processing speed as a mental capacity. *Acta Psychologica, 86,* 199-225.

Kaizer, F., Korner-Bitensky, N., Mayo, N., Becker, R., & Coopersmith, H. (1988). Response time of stroke patients to a visual stimulus. *Stroke, 19,* 335–339.

Karnath, H.-O. (1988). Deficits of attention in acute and recovered visual hemi-neglect. *Neuropsychologia, 26,* 27–43

Karnath, H.-O., Rennig, J., Johannsen, L., & Rorden, C. (2011). The anatomy underlying acute versus chronic spatial neglect: A longitudinal study. *Brain, 134,* 903-912.

Katz, N., Hartman-Maier, A., Ring, H., & Soroker, N. (1999). Functional disability and rehabilitation outcome in right hemisphere damaged patients with and without unilateral spatial neglect. *Archives of Physical Medicine and Rehabilitation, 80*, 379-384.

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

Kotila, M., Niemi, M., & Laaksonen, R. (1986). Four-year prognosis of stroke patients with visuospatial inattention. *Scandinavian Journal of Rehabilitation Medicine, 18*, 177-179.

Làdavas, E. (1987). Is the hemispatial deficit produced by right parietal lobe damage associated with retinal or gravitational co-ordinates? *Brain, 110,* 167–180.

Làdavas, E., Petronio, A., & Umiltà, C. (1990). The deployment of visual attention in the intact field of hemineglect patients. *Cortex, 26,* 307–317.

Laska., A. C., Hellblom, A., Murray, V., Kahan, T., & Von Arbin, M. (2001). Aphasia in acute stroke and relation to outcome. *Journal of Internal Medicine, 249,* 413-422. doi:10.1046/j.1365-2796.2001.00812.x

Levine, D. N., Warach, J. D., Benowitz, L., & Calvanio, R. (1986). Left spatial neglect: Effects of lesion size and premorbid brain atrophy on severity and recovery following right cerebral infarction. *Neurology, 36,* 362-366.

Levy, D., Blizzard, R. A., Halligan, P. W., & Stone, S. P. (1995). Fluctuations in visual neglect after stroke? *European Neurology, 35,* 341-343.

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). *Neuropsychological assessment* (5th ed). New York, NY: Oxford University Press.

Lézniak, M., Bak, T., Czepiel, W., Seniów, J., & Członkowska. (2008). Frequency and prognostic value of cognitive disorders in stroke patients. *Dementia and Geriatric Cognitive Disorders, 26,* 356-363. doi:10.1159/000162262

Lindell, A. B., Jalas, M. J., Tenovuo, O., Brunila, T., Voeten, M. J. & Hamalainen, H. (2007). Clinical assessment of hemispatial neglect: Evaluation of different measures and dimensions. *Clinical Neuropsychology, 21,* 479-497.

Linden, T., Samuelsson, H., Skoog, I., & Blomstrand, C. (2005). Visual neglect and cognitive impairment in elderly patients late after stroke. *Acta Neurologica Scandinavica, 111,* 163-168.

Lindenstrøm, E., Boysen, G., Christiansen, L. W., Hansen, B. R., & Nielsen, P. W. (1991). Reliability of scandinavian neurological stroke scale. *Cerebrovascular Diseases*. *1*, 103-107

Lindley, R. I., Warlow, C. P., Wardlaw, J. M., Dennis, M. S., Slattery, J., & Sandercock, P. A. (1993). Interobserver reliability of a clinical classification of acute cerebral infarction. *Stroke, 24,* 1801-1804.

Lunven, M., Thiebaut De Shotten, M., Bourlon, C., Duret, C., Migliaccio, R., Rode, G., & Bartolomeo, P. (2015). White matter lesional predictors of chronic visual neglect: A longitudinal study. *Brain, 138,* 746-760.

Manly, T., Dove, A., Blows, S., George, M., Noonan, M., Teasdale, T., …Warburton, E. (2009). Assessment of unilateral spatial neglect: Scoring Star Cancellation performance from video recordings—Method, reliability, benefits, and normative data. *Neuropsychology, 23,* 519-528.

Marshall, J. C., & Halligan, P. W. (1989). When right goes left: An investigation of line bisection in a case of visual neglect. *Cortex, 25,* 503-515.

McHutchison, C. A., Cvoro, V., Makin, S., Chappell, F. M., Shuler, K., & Wardlaw, J. M. (2019). Functional, cognitive and physical outcomes 3 years after minor lacunar or cortical ischaemic stroke. *Journal of Neurology, Neurosurgery & Psychiatry, 90,* 436-443.

Murray, L. L. (2002). Attention deficits in aphasia: Presence, nature, assessment, and treatment. *Seminars in Speech and Language, 23,* 107-116. doi:10.1055/s-2002-24987

Nesi, M., Lucente, G., Nencini, P., Fancellu, L., & Inzitari, D. (2014). Aphasia predicts unfavorable outcome in mild ischemic stroke patients and prompts thrombolytic treatment. *Journal of Stroke and Cerebrovascular Diseases, 23,* 204-208.

Nijboer, T., Kollen, B. J., & Kwakkel, G. (2013). Time course of visuospatial neglect early after stroke: A longitudinal cohort study. *Cortex, 49,* 2021-2027.

Nurmi, L., Ruuskanen, E. I., Nurmi, M., Koivisto, A. M., Parkkila, A. K., Numminen, H., …Jehkonen, M. (2018). Occurence and recovery of different neglect-related symptoms in right hemisphere infarct patients during a 1-year follow-up. *Journal of the International Neuropsychological Society, 24,* 617-628.

Nys, G. M. S., van Zandvoort, M. J. E., de Kort, P. L. M., van der Worp, H. B., Jansen, B. P. W., Algra, A., …Kappelle, L. J. (2005). The prognostic value of domain-specific cognitive abilities in acute first-ever stroke. *Neurology, 64,* 821-827.

Ogden, J. A. (1987). The 'neglected' left hemisphere and its contribution to visuospatial neglect. In M. Jeannerod (Ed), *Neurophysiological and neuropsychological aspects of spatial neglect* (pp. 215-233). North-Holland: Elsevier Science.

Ortique, S., Viaud-Delmon, I., Michel, C. M., Blanke, O., Annoni, J. M., Pegna, A., …Landis, T. (2003). Pure imagery hemi-neglect of far space. *Neurology, 60,* 2000-2002.

Paolucci, S., Antonucci, G., Gialloreti, L. E., Traballesi, M., Lubich, S., Pratesi, L., & Palombi, L. (1996). Predicting stroke inpatient rehabilitation outcome: The prominent role of neuropsychological disorders, *European Neurology, 36***,** 385-390. doi:10.1159/000117298

Paolucci, S., Antonucci, G., Pratesi, L., Traballesi, M., Lubich, S., & Grasso, M. G. (1998). Functional outcome in stroke inpatient rehabilitation: Predicting no, low and high response patients. *Cerebrovascular Diseases, 8,* 228-234. doi:10.1159/000015856

Paolucci, S., Grasso, M. G., Antonucci, G., Bragoni, M., Troisi, E., Morelli, D., …Rizzi, F (2001). Mobility status after inpatient stroke rehabilitation: 1 year-follow-up and prognostic factors. *Archives of Physical Medicine and Rehabilitation, 82*, 2-8.

Paolucci, S., Grasso, M. G., Antonucci, G., Troisi, E., Morelli, D., Coiro, P., & Bragoi, M. (2000). One-year follow-up in stroke patients discharged from rehabilitation hospital. *Cerebrovascular Diseases, 10,* 25-32.

Patel, M., Coshall, C., Rudd, A., & Wolfe, C. D. A. (2003). Natural history of cognitive impairment after stroke and factors associated with its recovery. *Clinical Rehabilitation, 17,* 158-166.

Patel, M. D., Tilling, K., Lawrence, E., Rudd, A. G., Wolfe, C. D. A., & McKevitt, C. (2006). Relationships between long-term stroke disability, handicap and health-related quality of life. *Age and Aging, 35,* 273-279.

Pedersen, P. M., Jorgensen, H. S., Nakayama, H., Raaschou, H. O., & Olsen, T. S. (1995). Aphasia in acute stroke: Incidence, determinants, and recovery. *Annals of Neurology, 38,* 659-66. doi:10.1002/ana.410380416

Pedersen, P. M., Jorgensen, H. S., Nakayama, H., Raaschou, H. O., & Olsen, T. S. (1996). The impact of aphasia on ADL and social activities after stroke: The Copenhagen stroke study. *Neurorehabilitation and Neural Repair, 10,* 91-96.

Pedersen, P. M., Jorgensen, H. S., Nakayama, H., Raaschou, H. O., & Olsen, T. S. (1997). Hemineglect in acute stroke--incidence and prognostic implications. The Copenhagen Stroke Study. *American Journal of Physical Medicine & Rehabilitation*, *76,* 122-127.

Pizzamiglio, L., Guariglia, C., Nico, D., & Padovani, A. (1993). Two separate systems for space cognition. In W. J. M. Levelt (Eds.), *Advanced psycholinguistics: A bressanone retrospective for Giovanni B. Flores D'Arcais* (pp. 157-162). Nijmegen, NL.

Posner, M. I., & Rafal, R. D. (1987). Cognitive theories of attention and the rehabilitation of attentional deficits. In M. J. Meier, A. L. Benton, & L. Diller (Eds.), *Neuropsychological rehabilitation* (pp. 182–201). Edinburgh, UK: Churchill Livingstone.

Post, M. W., & de Witte, L. P. (2003). Good inter-rater reliability of the Frenchay Activities Index in stroke patients. *Clinical Rehabilitation, 17,* 548-552.

Ramsey, L., Siegel, J., Lang, C., Strube, M., Shulman, G., & Corbetta, M. (2017). Behavioural clusters and predictors of performance during recovery from stroke. *Nature Human Behaviour*, *1*, 1-10.

Rasquin, S. M. C., Verhey, F. R. J., Lousberg, R., Winkens, I., & Lodder, J. (2002). Vascular cognitive disorders: Memory, mental speed and cognitive flexibility after stroke. *Journal of the Neurological Sciences, 203-204,* 115-119.

Redfors, P., Hofgren, C., Eriksson, I., Holmegaard, L., Samuelsson, H., & Jood, K. (2014). The Barrow Neurological Institute Screen for Higher Cerebral Functions in cognitive screening after stroke. *Journal of Stroke & Cerebrovascular Diseases, 23,* 349-355.

Redfors, P., Jood, K., Holmegaard, L., Rosengren, A., Blomstrand, C., & Jern, C. (2012). Stroke subtype predicts outcome in young and middle-aged stroke sufferers. *Acta Neurologica Scandinavia, 126*, 329-335.

Rengachary, J., d'Avossa, G., Sapir, A., Shulman, G. L., & Corbetta, M. (2009). Is the Posner reaction time test more accurate than clinical tests in detecting left neglect in acute and chronic stroke? *Archives of Physical Medicine and Rehabilitation, 90,* 2081-2088.

Rengachary, J., He, B. J., Shulman, G. L., & Corbetta, M. A. (2011). A behavioral analysis of spatial neglect and its recovery after stroke. *Frontiers in Human Neuroscience, 5,* 29.

Ringman, J. M., Saver, J. L., Woolson, R. F., Clarke, W. R., & Adams, H. P. (2004). Frequency, risk factors, anatomy, and course of unilateral neglect in an acute stroke cohort. *Neurology, 63,* 468-474.

Robertson, I. H. (1993). The relationship between lateralised and non-lateralised attentional deficits in unilateral neglect. In I.H. Robertson & J.C. Marshall (Eds.), Unilateral neglect: Clinical and experimental studies. *Brain damage, behaviour & cognition series* (pp. 257-275). Hillsdale, NJ: Lawrence Erlbaum.

Robertson, I. H. (2001). Do we need the "lateral" in unilateral neglect? Spatially nonselective attention deficits in unilateral neglect and their implications for rehabilitation. *NeuroImage, 14* (1 Pt 2), S85-90.

Robertson, I.H., Tegner, R., Tham, K., Lo, A., & Nimmo-Smith, I. (1995). Sustained attention training for unilateral neglect: Theoretical and rehabilitation implications. *Journal of Clinical and Experimental Neuropsychology, 17*, 416-430.

Rizzo, M., Anderson, S. W., Dawson, J., Myers, R., & Ball, K. (2000). Visual attention impairments in Alzheimer's disease. *Neurology, 23,* 1954-1959.

Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review,103,* 403-428.

Samuelsson, H. (1997). *Visuospatial neglect. Attentional deficits and anatomical correlates* (Unpublished doctoral dissertation). University of Gothenburg, Sweden.

Samuelsson, H., Hjelmquist, E., Jensen, C., Ekholm, S., & Blomstrand, C. (1998). Nonlateralized attentional deficits: An important component behind persisting visuospatial neglect? *Journal of Clinical and Experimental Neuropsychology, 20,* 73-78.

Samuelsson, H., Hjelmquist, E., Jensen, C., & Blomstrand, C. (2002). Search patterns in a verbally reported visual scanning test in patients showing spatial neglect. *Journal of the International Neuropsychological Society, 8,* 382-394.

Samuelsson, H., Hjelmquist, E., Naver, H., & Blomstrand, C. (1995). Different criteria in the assessment of visuospatial neglect. *Journal of Neurology, Neurosurgery, and Psychiatry, 58,* 114-115.

Schaapsmeerders, P., Maaijwee, N. A., van Djik, E. J., Rutten-Jacobs, L. C., Arntz, R. M., Schoonderwaldt, H. C., …de Leeuw, F-E. (2013). Long-term cognitive impairment after first-ever ischemic stroke in young adults. *Stroke, 44,* 1621-1628.

Schuling, J., de Haan, R., Limburg, M., & Groenier, K. H. (1993). The Frenchay Activities Index. Assessment of functional status in stroke patients. *Stroke, 24,* 1173-1177.

Small, M., & Ellis, S. (1994). Brief remission periods in visuospatial neglect: Evidence from long-term follow-up. *European Neurology, 34,* 147-154.

Smania, N., Martin, M. C., Gambina, G., Tomelleri, G., Palamara, A., Natale, E., & Marzi, C. A. (1998). The spatial distribution of visual attention in hemineglect and extinction patients. *Brain, 121,* 1759–1770.

Stein, M. S., Kilbride, C., & Reynolds, F. A. (2016). What are the functional outcomes of right hemisphere stroke patients with or without hemi-inattention complications? A critical narrative review and suggestions for further research. *Disability and Rehabilitation, 38,* 315-328. doi:10.3109/09638288.2015.1037865

Stone, S. P.., Halligan, P. W., Wilson, B., Greenwood, R. J., & Marshall, J. C. (1991). Performance of age-matched controls on a battery of visuo-spatial neglect tests. *Journal of Neurology, Neurosurgery, & Psychiatry, 54,* 341-344.

Stone, S. P., Wilson, B., Wroot, A., Halligan, P. W., Lange, L. S., Marshall, J. C., & Greenwood, R. J. (1991). The assessment of visuo-spatial neglect after acute stroke. *Journal of Neurology, Neurosurgery, and Psychiatry, 54,* 345-350.

Stone S. P., Halligan, P. W., & Greenwood, R. J. (1993). The incidence of neglect phenomena and related disorders in patients with an acute right or left hemisphere stroke. *Age Aging, 22*, 46-52. doi:10.1093/ageing/22.1.46

Su, C. Y., Wuang, Y. P., Lin, Y. H., & Su, J. H. (2015). The role of processing speed in post-stroke cognitive dysfunction. *Archives of Clinical Neuropsychology, 30,* 148-160.

Suchan, J., & Karnath, H. (2011). Spatial orienting by left hemisphere language areas: A relict from the past? *Brain, 134*, 3059-3070.

Suchan, J., Rorden, C., & Karnath, H-O. (2012). Neglect severity after left and right brain damage. *Neuropsychologia, 50,* 1136-1141. doi:10.1016/j.neuropsychologia.2011.12.018

Sunderland, A., Wade, D. T., & Hewer, L. R. (1987). The natural history of visual neglect after stroke: Indications from two methods of assessment. *International Disability Studies, 9,* 55-59. doi:10.3109/03790798709166235

Sweet, L. H. (2011). Information processing speed. In: Kreutzer J. S., DeLuca J., Caplan B. (eds). *Encyclopedia of Clinical Neuropsychology.* New York, NY: Springer.

Synhaeve, N. E., Schaapsmeerders, P., Arntz, R. M., Maaijwee, N. A., Rutten-Jacobs, L. C. Schoonderwaldt, H. C., …van Djik, E. J. (2015). Cognitive performance and poor long-term functional outcome after young stroke. *Neurology, 85,* 776-782.

Taub, N. A., Wolfe, C. D. A., Richardson, E., & Burney, P. G. J. (1994). Predicting the disability of first-time stroke sufferers at 1 year: 12-months follow-up of a population-based cohort in southeast England. *Stroke, 25,* 352-357.

Thommessen, B., Thoresen, G. E., Bautz-Holter, E., & Laake, K. (2002). Validity of the aphasia item from the Scandinavian Stroke Scale. *Cerebrovascular Diseases, 13,* 184-186.

Ting, D. S. J., Pollock, A., Dutton, G. N., Doubal, F. N., Ting, D. S. W., Thompson, M., & Dhillon, B. (2011). Visual neglect following stroke: Current concepts and future focus. *Survey of Ophthalmology, 56,* 114-134. doi:10.1016/j.survophthal.2010.08.001

Tsirlin, I., Dupierrix, E., Chokron, S., Coquillart, S., & Ohlmann, T. (2009). Uses of virtual reality for diagnosis, rehabilitation and study of unilateral spatial neglect: review and analysis. *CyberPsychology & Behavior, 12,* 175-181. doi:10.1089/cpb.2008.0208

Tsouli, S., Kyritsis, A. P., Tsagalis, G., Virvidaki, E., & Vemmos, K. N. (2009). Significance of aphasia after first-ever acute stroke: Impact on early and late outcomes. *Neuroepidemiology, 33,* 96-102.

Umarova, R. M., Beume, L., Reisert, M., Kaller, C. P., Klöppel, S., Mader, I., …Weiller, C. (2017). Distinct white matter alterations following severe stroke: Longitudinal DTI study in neglect. *Neurology, 88,* 1546-1555.

Vallar, G. (1998). Spatial hemineglect in humans. *Trends in Cognitive Sciences, 2,* 87–97. doi:10.1016/S1364-6613(98)01145-0

van Swieten, J. C., Koudstaal, P. J., Visser, M. C., Schouten, H. J., & van Gijn, J. (1988). Interobserver agreement for the assessment of handicap in stroke patients. *Stroke, 19*, 604-607.

Viken, J. I., Jood, K., Jern, C., Blomstrand, C., & Samuelsson, H. (2014). Ipsilesional bias and processing speed are important predictors of functional dependency in the neglect phenomenon after a right hemisphere stroke. *The Clinical Neuropsychologist, 28,* 974-993.

Wade, D. T., Hewer, R. L., David, R. M., & Enderby, P. M. (1986). Aphasia after stroke: Natural history and associated deficits. *Journal of Neurology, Neurosurgery & Psychiatry, 49*, 11–16.

Wade, D. T., Wood, V. A., & Hewer, R. L., (1988). Recovery of cognitive function soon after stroke: A study of visual neglect, attention span and verbal recall. *Journal of Neurology, Neurosurgery, and Psychiatry, 51,* 10-13.

Wallin, A., Nordlund, A., Jonsson, M., Blennow, K., Zetterberg, H., Öhrfelt, A., …Bjerke, M. (2016). Alzheimer's disease – subcortical vascular disease spectrum in a hospital-based setting: Overview of results from the Gothenburg MCI and dementia studies. *Journal of Cerebral Blood Flow & Metabolism, 36,* 95-113.

Wardlaw, J. M., Dennis, M. S., Lindley, R. I., Sellar, R. J., & Warlow, C. P. (1996). The validity of a simple clinical classification of acute ischaemic stroke. *Journal of Neurology, 243,* 274-279.

Willmott, C., Ponsford, J., Hocking, C., & Schönberger, M. (2009). Factors contributing to attentional impairments after traumatic brain injury. *Neuropsychology, 23,* 423-432.

Wilson, B., Cockburn, J., & Halligan, P. W. (1987). *The behavioural inattention test.* Bury St. Edmunds, UK: Thames Valley Test Company.

Winkens, I., Van Heugten, C. M., Fasotti, L., Duits, A. A., &Wade, D. T. (2006). Manifestations of mental slowness in the daily life of patients with stroke: A qualitative study. *Clinical Rehabilitation, 20,* 827-834.

Young, J., Bogle, S., & Forster, A. (2001). Determinants of social outcome measured by the Frenchay Activities Index at one year after stroke onset. *Cerebrovascular Diseases, 14*, 114-120.

APPENDIX

I. Gerafi, J., Samuelsson, H., Viken, J. I., Blomgren, C., Claesson, L., Kallio, S., Jern, C., Blomstrand, C., & Jood, K. (2017). Neglect and aphasia in the acute phase as predictors of functional outcome 7 years after ischemic stroke. *European Journal of Neurology, 24,* 1407-1415. doi:10.1111/ene.13406

II. Gerafi, J., Samuelsson, H., Viken, J. I., Blomgren, C., Claesson, L., Kallio, S., Jern, C., Blomstrand, C., & Jood, K. Visuospatial inattention following a left hemispheric stroke predicts long-term functional outcome. *Manuscript unpublished.*

III. Gerafi, J., Samuelsson, H., Viken, J. I., Jern, C., Blomstrand, C., & Jood, K. (2019). The presence and prediction of lateralized inattention 7 years post-stroke. *Acta Neurologica Scandinavica. Manuscript accepted pending minor revision.*

IV. Gerafi, J., Samuelsson, H., Viken, J. I., Jern, C., Blomstrand, C., & Jood, K. Patterns of change in visual processing speed after ischemic stroke: A long-term descriptive study. *Manuscript unpublished.*