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EXECUTIVE AND MEMORY IMPAIRMENTS AFTER FIRST-EVER CEREBRAL INFARCTION

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DOCTORAL DISSERTATION

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ABSTRACT

Strokes are one of the leading causes of loss of quality years of life. Most strokes befall older people, but one-fourth of stroke patients are working aged. Incidence of stroke is increasing among the working-aged population, and more information is needed on post-stroke profiles in this patient group. Younger stroke patients also have fewer age-related, non-stroke cognitive changes compared with the elderly, which allows a better inspection of the effects of stroke itself and the associations between lesion location and cognitive function.

In the present studies, executive functions and memory performance were examined in a well-defined working-aged stroke cohort. First, differences in neuropsychological profiles after cortical and subcortical strokes were examined. Second, associations between executive dysfunction and memory problems were studied. Finally, changes in domain-specific functioning during a 2-year follow-up period were examined.

The studied cohort consisted of 230 first-ever stroke patients, aged 18–65 years, from two central hospitals in Finland. The patients were examined neuropsychologically, covering multiple cognitive domains, as well as neurologically. In the first study, 132 patients whose strokes were visible in clinical brain scanning and involved only cortical or only subcortical areas were included, and differences between these groups at baseline (within the first weeks post stroke) and 6-month examinations were evaluated. In the second study, 179 patients who displayed no recurrent brain damage and possessed sufficient language abilities were included, and differences at 6-month and 2-year examinations between executively impaired and intact patients' memory performance were evaluated. In the third study, all 153 patients who participated in baseline, 6-month and 2-year examinations and did not have recurrent brain damage were included, and recovery of cognitive functioning throughout the follow-up was evaluated.

In this working-aged patient cohort, most cognitive improvement occurred between the baseline and 6 months, and little cognitive recovery was subsequently found. Cognitive impairments were common in thorough neuropsychological examination, even in patients demonstrating good recovery in neurological scales. Impairments in psychomotor speed and executive functions were the most common domain-specific impairments throughout the follow-up. Executive dysfunction was associated with impaired performance in memory tasks that required active use of memory strategies for up to 2 years post stroke. No differences were found in the frequency of executive dysfunction between subcortical and cortical strokes. More memory

problems and loss of psychomotor speed arose after subcortical than cortical strokes.

In terms of practical implications, the present studies demonstrated that long-lasting cognitive impairments are common post stroke, even in relatively well-recovered working-aged stroke patients. Early and detailed neuropsychological examinations are essential for finding cognitively impaired patients, as even small subcortical strokes can induce long-lasting impairments that may affect, for example, work performance. As cognitive recovery seems most prominent early post stroke, neuropsychological rehabilitation should also begin early to guide the recovery. Based on the present results, cognitive problems following stroke may be long lasting, and thus the need for rehabilitation should be evaluated throughout patient follow-up, and rehabilitation should be provided for a sufficiently long period.

TIIVISTELMÄ

Aivoinfarktien vuoksi menetetään huomattava määrä laatupainotteisia elinvuosia. Vaikka suurin osa aivoinfarktiin sairastuneista on ikääntyneitä, neljännes on työikäisiä. Työikäisten sairastuvuus on lisääntymässä korkean työtulon maissa ja tarkempaa tietoa tämän potilasryhmän kognitiivisesta oireprofiilista tarvitaankin lisää. Nuoremmilla aivoinfarktiin sairastuneilla on myös vähemmän ikään liittyviä aivomuutoksia kuin ikääntyneillä, mikä mahdollistaa tarkemman aivoinfarktin vaikutusten tutkimisen ja aivoinfarktin sijainnin ja kognitiivisten oireiden yhteyksien tutkimisen.

Tässä tutkimuksessa tarkasteltiin toiminnanohjausta ja muistisuoriutumista tarkkaan rajatulla työikäisellä aivoinfarktipotilasaineistolla. Ensin tarkasteltiin neuropsykologista oireprofiilia kortikaalisten (aivokuoren) ja subkortikaalisten (aivokuoren alaisten) aivoinfarktien jälkeen. Toiseksi tarkasteltiin toiminnanohjauksen ja muistisuoriutumisen yhteyksiä. Viimeiseksi tarkasteltiin kognition eri osa-alueiden toiminnan muutoksia kahden vuoden seurannassa.

Tutkimuksen potilaskohortti koostui kahdesta suomalaisesta keskussairaalasta kerätystä 230 ensimmäiseen diagnosoituun aivoinfarktiin sairastuneesta 18–65-vuotiaasta henkilöstä. Potilaat tutkittiin neuropsykologisesti kattaen useita kognitiivisia osa-alueita sekä lisäksi neurologisesti. Ensimmäiseen osatutkimukseen valittiin ne 132 potilasta, joiden aivoinfarktit kuvantuivat kliinisissä tutkimuksissa ja rajautuivat joko kortikaalisesti tai subkortikaalisesti. Näiden ryhmien eroja verrattiin alkuvaiheen (sairastumista seuranneet ensimmäiset viikot) ja kuuden kuukauden tutkimuksissa. Toiseen osatutkimukseen valittiin ne 179 potilasta, joilla ei seurannassa ilmennyt uusia aivovaurioita, ja joiden kielelliset taidot olivat riittävät kuuden kuukauden ja kahden vuoden seurantatutkimuksessa. Potilaat jaettiin toiminnanohjaukseltaan heikentyneisiin ja normaalisti suoriutuviin ja näiden ryhmien eroja tutkittiin. Kolmanteen osatutkimukseen valittiin kaikki ne 153 potilasta, jotka osallistuivat alkuvaiheen, kuuden kuukauden ja kahden vuoden tutkimukseen, ja joilla ei seurannassa ilmennyt uusia aivovaurioita. Kolmannessa osatutkimuksessa tarkasteltiin kognition kuntoutumista seuranta-aikana.

Suurin osa kognitiivisesta kuntoutumisesta tapahtui tutkitussa potilasjoukossa alkuvaiheen ja kuuden kuukauden välillä, jonka jälkeen havaittiin vain vähän kognitiivisia muutoksia. Kognitiivinen heikentyminen oli yleistä tarkoissa neuropsykologisissa tutkimuksissa niilläkin potilailla, joiden todettiin olevan hyvin toipuneita neurologisten mittareiden perusteella. Psykomotorinen hidastuneisuus ja toiminnanohjauksen vaikeudet olivat tyypillisimpiä kognitiivisia oireita läpi seuranta-ajan. Toiminnanohjauksen vaikeudet olivat yhteydessä heikentyneeseen muistisuoriutumiseen tehtävissä, joissa tarvittiin aktiivista muististategioiden

käyttöä. Toiminnanohjauksen vaikeuksien yleisyydessä ei havaittu eroa subkortikaalisten ja kortikaalisten infarktien jälkeen, sen sijaan muistivaikeuksia ja psykomotorista hidastumista havaittiin runsaammin subkortikaalisten kuin kortikaalisten infarktien jälkeen.

Pitkäkestoiset kognitiiviset oireet ovat yleisiä jopa neurologisesti hyvin toipuneilla työikäisillä aivoinfarktin sairastaneilla potilailla. Tarkka neuropsykologinen tutkimus nopeasti aivoinfarktin jälkeen on tärkeää, jotta voidaan erottaa potilaat, joilla on kognitiivisia häiriöitä, jotka voivat vaikuttaa esimerkiksi työssä pärjäämiseen. Kognitiivisien vaikeuksien profiilia tai vaikeusastetta ei voi päätellä esimerkiksi infarktin kliinisten tietojen kuten sijainnin perusteella. Neuropsykologinen kuntoutus tulisi tulosten perusteella aloittaa nopeasti, sillä suurin osa kognitiivisesta kuntoutumisesta tapahtuu puolen vuoden kuluessa sairastumisesta. Tämän tutkimuksen perusteella kuntoutustarvetta tulee arvioida myös myöhemmässä vaiheessa ja kuntoutusta tulee tarjota riittävän pitkään, sillä tutkimuksessa havaittiin, että kognitiiviset oireet ovat pitkäkestoisia.

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CONTENTS

Abstract....3

Tiivistelmä....5

Acknowledgements....7

Contents....8

List of original publications....10

Abbreviations....11

1 Introduction....13

1.1 Stroke in general....13

1.2 Overall and domain-specific cognitive profiles after stroke....14

1.2.1 Cognitive status early post stroke and at subacute state....14

1.2.2 Recovery of cognitive functions....15

1.2.3 Cognitive status at later states after stroke....16

1.3 Subcortical and cortical stroke and cognitive impairments....16

1.4 Associations between executive functions and memory....18

1.5 Stroke in the working aged....19

2 Aims of the present research....20

3 Methods....21

3.1 Participants....21

3.1.1 Study I subpopulation....22

3.1.2 Study II subpopulation....22

3.1.3 Study III subpopulation....22

3.2 Neuropsychological examination....23

3.2.1 Neuropsychological domains and data transformations in Study I....24

3.2.2 Neuropsychological domains and data transformations in Study II 24

3.2.3 Neuropsychological domains and data transformations in Study III 25

3.3 Clinical and neurological examination, medical records and registry data 26

3.4 Statistical Analyses 27

4 Results 28

4.1 Demographics 28

4.2 Comparison of subcortical and cortical strokes (Study I) 29

4.3 Associations of executive dysfunction and memory problems (Study II) 30

4.4 Recovery of domain-specific cognitive functioning in 2-year follow-up (Study III) 34

5 Discussion 40

5.1 Overall cognitive impairment, mood and return to work after stroke 40

5.2 Executive dysfunction after stroke 42

5.3 Memory dysfunction after stroke 44

5.4 Associations between executive and memory dysfunction after stroke 46

5.5 Dysfunction in other cognitive domains after stroke 47

5.6 Methodological considerations 48

5.7 Concluding notes 50

References 52

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications that will be referred to as Study I–III in the text:

Study I. Turunen, K. E. A., Kauranen, T. V., Laari, S. P. K., Mustanoja, S. M., Tatlisumak, T., & Poutiainen, E. T. (2013). Cognitive deficits after subcortical infarction are comparable with deficits after cortical infarction. *European Journal of Neurology*, *20*, 286–292.

Study II. Turunen, K. E. A., Laari, S. P. K., Kauranen, T. V., Mustanoja, S., Tatlisumak, T., & Poutiainen, E. (2016). Executive impairment is associated with impaired memory performance in working-aged stroke patients. *Journal of the International Neuropsychological Society*, *22*, 551–560.

Study III. Turunen, K. E. A., Laari, S. P. K., Kauranen, T. V., Uimonen, J., Mustanoja, S., Tatlisumak, T., & Poutiainen, E. (2018). Domain-specific cognitive recovery after first-ever stroke: A 2-year follow-up. *Journal of the International Neuropsychological Society*, *24*, 117–127.

ABBREVIATIONS

ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
BRVRT	Benton Revised Visual Retention Test
CT	Computed tomography
FLAIR	Fluid-attenuated inversion recovery
ICI	Inferential confidence intervals
LM I / LM II	Logical Memory tests I and II
MANOVA	Multivariate analysis of variance
MANCOVA	Multivariate analysis of covariance
MRI	Magnetic resonance imaging
mRS	Modified Rankin scale
NIHSS	National Institutes of Health stroke scale
POMS	Profile of mood states
SPSS	Statistical package for social sciences
TM A	Trail Making Test part A
TM B	Trail Making Test part B
TOAST	Trial of Org 10172 in acute stroke treatment
WAIS-III	Wechsler adult intelligence scale, the third edition
WMS-R	Wechsler memory scale revised

1 INTRODUCTION

1.1 STROKE IN GENERAL

A stroke is an episode of acute neurological dysfunction that is caused by the dysfunction of blood vessels in the central nervous system, and ischemic strokes are specifically caused by infarctions in cerebral, spinal and retinal areas (Sacco et al., 2013). Strokes likely cause the largest losses of quality years of life (Davenport & Dennis, 2000). In Finnish studies, 50–70 % of stroke patients have recovered to be independent within three months post stroke, and only 5 % remain hospitalized for an entire year (Brain infarction and TIA: Current Care Guidelines, 2016).

Around 80 % of strokes in Western countries are brain infarctions (Davenport & Dennis, 2000). Brain infarctions emerge in carotid areas in 80 % of stroke patients and in vertebrobasilar areas in 10–20 % of stroke patients (Brain infarction and TIA: Current Care Guidelines, 2016). Ischemic strokes can be divided to five subtypes (Adams et al., 1993): large-artery atherosclerosis (21 % of all ischemic stroke patients and 8 % of patients under 50 years), cardioembolism (26 % and 20 %), small-vessel occlusion (21 % and 14 %), stroke of other determined etiology (4 % and 25 %) and stroke of undetermined etiology (23 % and 31 %; Brain infarction and TIA: Current Care Guidelines, 2016). Men are more likely to suffer from strokes in all age groups (Hyvärinen et al., 2010).

Cognitive outcomes after strokes are often measured with short screening methods (Tang et al., 2018). In a recent review, the longitudinal course of post-stroke screened cognitive functioning seemed variable, as deterioration, stability and improvement were all observed (Tang et al., 2018). However, particularly in younger patients and with milder strokes, neurological or cognitive screening methods have not sufficiently predicted cognitive dysfunction (Bour, Rasquin, Boreas, Limburg, & Verhey, 2010; Kauranen et al., 2014; Nys, van Zandvoort, de Kort, Jansen, Kappelle, & de Haan, 2005).

Post-stroke depression is common, with around one out of three stroke survivors developing it (Towfighi et al., 2017). Cognitive impairment is among the most consistent predictors of post-stroke depression, although variability in the related literature is high (Towfighi et al., 2017). Associations between mood changes and cognitive impairment, however, are not always examined.

1.2 OVERALL AND DOMAIN-SPECIFIC COGNITIVE PROFILES AFTER STROKE

1.2.1 COGNITIVE STATUS EARLY POST STROKE AND AT SUBACUTE STATE

Notable post-stroke cognitive impairments are observed in studies with more thorough neuropsychological examinations. Early after suffering a first-ever stroke, cognitive dysfunction in at least one cognitive domain is shown in at least half of stroke patients (Nys et al., 2007; Rasquin, Verhey, Lousberg, Winkens, & Lodder, 2002). The most common cognitive domains to become impaired early post stroke are processing speed, executive functioning and cognitive flexibility, working memory, and visual perception and construction (Hurford, Charidimou, Fox, Cipolotti, & Werring, 2013; Jaillard, Naegele, Trabucco-Miguel, LeBas, & Hommel, 2009; Nys et al., 2007; Pinter et al., 2019; Rasquin et al., 2002). Only studies using more thorough neuropsychological examination are reported here. The patient samples, however, have not been limited to the working aged (Hurford et al., 2013; A. Jaillard et al., 2009; Nys et al., 2007; Rasquin et al., 2002) or to patients with first-ever strokes (Hurford et al., 2013; Pinter et al., 2019).

Executive functions include multiple cognitive processes that are crucial for adaptive behavior in novel situations; subcomponents of executive functions include volition, goal formation and planning, and effective and purposive action (Diamond, 2013; Jurado & Rosselli, 2007). As many subcomponents exist, many types of measures are needed to examine executive functions and related behaviors. Commonly studied subcomponents include set shifting, updating information, inhibiting prepotent responses and working memory (Diamond, 2013; Miyake et al., 2000). Executive dysfunction, or disturbances in cognitive flexibility, are observed in up to half of patients early post first-ever stroke (Jaillard et al., 2009; Nys et al., 2007; Rasquin et al., 2002) and early after stroke in young patients (Pinter et al., 2019).

Memory problems can markedly limit patients' everyday functioning and ability to work. Although memory problems are often observed post stroke, different procedures to detect memory impairment have been used. In examinations performed within the first month post stroke, the verbal memory domain has been impaired in up to one-fourth of patients (Nys et al., 2007; Rasquin et al., 2002), and the visual memory domain demonstrates a similar impairment rate (Nys et al., 2007). Higher impairment rates have been reported as well, with at least one verbal or visual memory task impaired in two in five patients (Jaillard et al., 2009).

In the subacute state – around 2–4 months post stroke – impaired processing speed is common in patients of all ages (Hochstenbach, Mulder, van Limbeek, Donders, & Schoonderwaldt, 1998; Sachdev, Brodaty, Valenzuela, Lorentz, Looi et al., 2004; Tatemichi et al., 1994). Attentional and executive disorders are also common, observed in as many as half of patients

in neuropsychological examination (Hochstenbach et al., 1998; Sachdev, Brodaty, Valenzuela, Lorentz, Looi et al., 2004; Srikanth et al., 2003; Tatemichi et al., 1994). Memory disorders can be common in the subacute states as well and were reported to occur in up to half of stroke patients in earlier studies (Hochstenbach et al., 1998; Kotila, Waltimo, Niemi, Laaksonen, & Lempinen, 1984; Tatemichi et al., 1994). In more recent studies, however, no differences in memory performance have been observed between stroke patients and control groups in the subacute state (Sachdev, Brodaty, Valenzuela, Lorentz, Looi et al., 2004; Srikanth et al., 2003).

1.2.2 RECOVERY OF COGNITIVE FUNCTIONS

Neuropsychologically evaluated domain-specific cognitive impairments alleviate to some extent after early states in first-ever stroke patients, not restricted to the working aged (Nys, van Zandvoort, de Kort, van der Worp et al., 2005; Rasquin et al., 2002; van Zandvoort, Kessels, Nys, de Haan, & Kappelle, 2005). Compared with the early states, performance improves in up to half of patients in different cognitive domains within 6 months (Rasquin et al., 2002), cognitively impaired patients improve in all cognitive domains compared with control groups within 6–10 months (Nys, van Zandvoort, de Kort, van der Worp et al., 2005), and fewer patients were severely impaired in the majority of neuropsychological tasks within 1–2 years (van Zandvoort et al., 2005).

Cognitive impairments early post stroke predict similar cognitive impairments at 6–10 months post stroke (Nys, van Zandvoort, de Kort, Jansen, van der Worp et al., 2005), and the cognitive symptom profile remains stable during follow-up between early states and 1–2 years (van Zandvoort et al., 2005) in neuropsychological evaluations. Evidence on which cognitive domains most recover between acute states and follow-up is mixed. In one study, visual attention and construction and visual memory recovered most, whereas the recovery of basic language functions and abstract reasoning was the least common (Nys, van Zandvoort, de Kort, Jansen, van der Worp et al., 2005). Another study demonstrated trends of recovery in perceptual skills, speed and attention, and executive functions, but not in visual or verbal memory, after the acute state of stroke with separate patient groups of all ages at different time points (Hurford et al., 2013).

Information on neuropsychologically evaluated cognitive recovery between subacute states and later follow-ups (1–2 years) is mixed. Cognitive dysfunction alleviated – the most in attention, and the least in memory – in one study including patients of all ages (Hochstenbach, den Otter, & Mulder, 2003). However, only a small subgroup of patients demonstrated recovery, and most remained cognitively the same, while some deteriorated (Hochstenbach et al., 2003). In another study with patients of all ages, stroke patients' verbal memory performance and visuoconstructive functioning deteriorated compared with control groups, although some of the apparent

deterioration may have been due to the improving performance of control groups (Sachdev, Brodaty, Valenzuela, Lorenz, & Koschera, 2004).

Recovery of domain-specific cognitive impairment after 6 months post stroke has remained relatively unstudied. In one study, the performance of most patients remained stable between 6 months and 1 year in individual neuropsychological tasks (Rasquin, Lodder et al., 2004). In a recent study with small numbers of patients, first-ever stroke patients' performance remained stable between 7 months and 10 years in most neuropsychological tasks (Elgh & Hu, 2019). The only neuropsychological task wherein patients' performance deteriorated between 7 months and 10 years post stroke was symbol searching, which indicates a slowing of performance after ten years' time (Elgh & Hu, 2019).

1.2.3 COGNITIVE STATUS AT LATER STATES AFTER STROKE

In examining overall cognitive status post stroke in follow-ups after 1–11 years, patients' cognitive performance is typically impaired when compared with control groups, in both young first-ever stroke patients (Schaapsmeerders et al., 2013) and in patients of all ages (Sachdev, Brodaty, Valenzuela, Lorenz, & Koschera, 2004). Furthermore, up to half of stroke patients of all ages perform below average in specific domains when compared with norms (Barker-Collo, Feigin, Parag, Lawes, & Senior, 2010).

Five years post stroke, stroke patients' impairment has been reported to be most pronounced in executive functions and processing speed, as one-third of patients were impaired in both (Barker-Collo et al., 2010). Eleven years post stroke, again, processing speed, as well as working memory, have been found to most likely be impaired, followed by impaired attention and executive functions (Schaapsmeerders et al., 2013). As with subacute state, memory was not observed to be pronouncedly impaired 5 years post stroke, as less than one-tenth of patients were impaired (Barker-Collo et al., 2010). However, according to a study, later, at 11 years post stroke, up to one-fourth of patients were impaired in immediate memory domain or delayed memory domain as well (Schaapsmeerders et al., 2013).

1.3 SUBCORTICAL AND CORTICAL STROKE AND COGNITIVE IMPAIRMENTS

Cognitive symptom profiles vary due to stroke location and size, as well as changes in brain functioning (Cumming, Marshall, & Lazar, 2013; Pohjasvaara, Ylikoski, Hietanen, Kalska, & Erkinjuntti, 2002). Stroke hemisphere is often shown to be associated with specific symptoms and overall cognitive functioning. Of specific symptoms, for example, neglect is more likely to occur after right-sided lesions (Caggiano & Jehkonen, 2018; Halligan, Fink, Marshall, & Vallar, 2003), and aphasia is associated with left-sided

lesions (Plowman, Hentz, & Ellis, 2012). The evidence for lateralized effects in cognitive outcome post stroke is mixed, as some studies identify more impairment after left-hemisphere strokes (Hochstenbach et al., 1998; Nys et al., 2007; Schaapsmeerders et al., 2013; van Zandvoort et al., 2005), whereas others reveal no significant differences between left- and right-hemisphere strokes (Arauz et al., 2014; Barker-Collo et al., 2012; Jaillard, Grand, Le Bas, & Hommel, 2010; Planton et al., 2011). Differences in cognitive profiles after subcortical and cortical strokes are less studied. In one study, when strokes were classified based on circulation location instead of hemispheric location, patients with anterior strokes were found more impaired in one-third of the neuropsychological measures used, compared with patients with strokes in other locations, whereas patients with posterior circulation strokes had the least impaired profile, and patients with lacunar strokes performed in between these groups (Barker-Collo et al., 2012).

Some evidence exists that patients with cortical strokes perform inferiorly to patients with subcortical strokes at early states. In one study, patients with strokes involving the cortex were more likely to be cognitively impaired overall than patients with exclusively subcortical strokes (Nys et al., 2007), and in another study, patients with territorial infarcts were more likely to be cognitively impaired than patients with lacunar infarcts that locate subcortically (Rasquin, Verhey, van Oostenbrugge, Lousberg, & Lodder, 2004). In one study with domain-specific subdivision, patients with cortical strokes performed inferiorly to patients with subcortical strokes in one of five cognitive domains (Wilde, 2010). However, superficial and deep strokes did not differ in predicting overall cognitive dysfunction in first-ever stroke patients, in another study (Jaillard et al., 2010).

Later post stroke, no differences have been found in cognitive performance between patients with subcortical versus cortical strokes at subacute state, either domain specifically (Hochstenbach et al., 1998) or overall (Arauz et al., 2014; Planton et al., 2011), nor have differences been found between patients with territorial versus lacunar strokes in the risk of overall cognitive impairment at 6 or 12 months post stroke (Rasquin, Verhey et al., 2004). Furthermore, domain-specific cognitive recovery between subcortical and cortical stroke patients does not differ between 3 months and 1 year (Hochstenbach et al., 2003). Only two of the previous studies compared specific cognitive domains between subcortical and cortical stroke patients (Hochstenbach et al., 2003; Wilde, 2010), while the others compared overall cognitive impairment. Furthermore, subcortical strokes are often smaller lacunes while cortical strokes may cover an entire vascular territory, and subcortical strokes are thus likely smaller than cortical strokes. The previous studies mentioned (Arauz et al., 2014; Hochstenbach et al., 1998; Jaillard et al., 2010; Nys et al., 2007; Planton et al., 2011; Wilde, 2010) did not consider the effects of stroke size when comparing cognitive performance between patients with subcortical and cortical strokes.

1.4 ASSOCIATIONS BETWEEN EXECUTIVE FUNCTIONS AND MEMORY

Frontal lobes are thought to be crucial in executive functions, and historically, executive dysfunction has been taken as a measure of frontal lobe dysfunction (Jurado & Rosselli, 2007; Stuss & Alexander, 2000). Executive functions should not, however, be used synonymously for frontal lobe functions (Stuss, 2011). Fronto-subcortical loops connect prefrontal areas to multiple subcortical areas, and the loops are shown to partake in executive control, which suggests the relevance of subcortical structures in executive control processes (Heyder, Suchan, & Daum, 2004).

However, through frontal lobes and their connections, executive functions are shown to contribute to memory functioning (Davidson, Troyer, & Moscovitch, 2006). Different types of strokes can cause different types of memory impairment (Lim & Alexander, 2009). A stroke can damage, for example, brain regions that are crucial for normal learning and thus also impair recall of memory material (Lim & Alexander, 2009). Patients with frontal lobe damage have problems in list learning when related words are used, particularly in tasks of free recall of the wordlist (Alexander, Stuss, & Gillingham, 2009; Lim & Alexander, 2009; Wheeler, Stuss, & Tulving, 1995). Patients with frontal lobe damage are also impaired in tasks requiring strategy usage or the spontaneous organization of memory material (Davidson et al., 2006; Gershberg & Shimamura, 1995).

Irrespective of brain dysfunction location, memory problems may also arise secondarily post stroke due to executive dysfunction (Lim & Alexander, 2009). Here, memory issues can be due to impaired retrieval from memory or difficulties in monitoring functioning, for example, in recognition tasks (Lim & Alexander, 2009). Direct associations between executive functioning and memory problems – without using the link through frontal lobes – have also been studied. Executive functioning is indeed associated with different sub-measures of list learning with related word lists, in studies with mixed patient samples (Brooks, Weaver, & Scialfa, 2006; Hill, Alosco, Bauer, & Tremont, 2012; Tremont, Halpert, Javorsky, & Stern, 2000; Tremont, Miele, Smith, & Westervelt, 2010). Lists with unrelated words have not been compared between executively impaired and intact patients, although these lists seem to provide even less inherent structure to support the learning process. It has been hypothesized that story recall provides more inherent structure than list learning (Tremont et al., 2000), but the evidence is mixed (Busch et al., 2005; Tremont et al., 2000; Tremont et al., 2010).

Associations of executive functioning with visual memory have been studied less than those with verbal memory in patient populations. In studies with mixed neurological and traumatic brain injury samples, executive dysfunction predicts some visual memory impairments (Busch et al., 2005; Temple, Davis, Silverman, & Tremont, 2006), and this association remains stable after controlling for severity of brain injury (Busch et al., 2005).

Baddeley (1996) has proposed that a phonological loop, visuo-spatial sketch pad and central executive constitute the working memory. The visuo-spatial sketch pad is suggested to rely largely on the central executive and to be more complex than the phonological loop (Baddeley, 1996). Furthermore, visual imagery and production are suggested to be less automatic than verbal production (Baddeley, 1996). Taken together, in this model, executive dysfunction may readily affect visual memory performance.

In addition to executive dysfunction, memory may also be impaired post stroke due to impaired general understanding (Lim & Alexander, 2009). Executive functions and memory correlate both with each other and with general intelligence (Duff, Schoenberg, Scott, & Adams, 2005). Previously, the efforts made to control for the effects of general intellect were generally minimal when studying the associations between executive functions and memory, despite the strong correlations (Duff et al., 2005).

1.5 STROKE IN THE WORKING AGED

Age is an important factor when evaluating functional outcome post stroke (Knoflach et al., 2012). Most stroke studies have concerned elderly patients, and the information on the prevalence of cognitive deficits is limited in the working aged. However, around one-fourth of stroke patients are working aged, under 65 years (Daniel, Wolfe, Busch, & McKevitt, 2009); in Finland in 2010, 21 % of stroke patients were in this age group (Brain infarction and TIA: Current Care Guidelines, 2016). Also, the incidence of stroke in younger patient groups is increasing in high-income countries (Béjot, Delpont, & Giroud, 2016; Brain infarction and TIA: Current Care Guidelines, 2016). Working-aged patients cause indirect costs due to loss of working years and increased use of social benefits and thus require special attention. Severity of cognitive impairment is a good predictor of return to work (Edwards, Kapoor, Linkewich, & Swartz, 2018; Kauranen et al., 2013). More information is needed on the cognitive profile of these younger stroke patients from early states on, through longer follow-up periods, to better predict return to work and guide rehabilitation efforts towards helping the patients return to working life.

2 AIMS OF THE PRESENT RESEARCH

The aim of the present thesis was to examine executive and memory functions post first-ever stroke in a working-aged cohort. Information is limited on cognitive profile post stroke among the working aged, as well as on possible cognitive changes after the most prominent recovery period early post stroke in stroke patients of all ages. As specific cognitive domains, for example, executive dysfunction and memory problems, have been reported to be common sequelae of stroke, the present study focused specifically on these symptoms. Furthermore, the associations between cognitive dysfunction and clinical aspects, such as lesion corticality, were studied.

In **Study I**, the aim was to assess differences in domain-specific cognitive deficits between patients with subcortical and cortical strokes. In clinical practice, subcortical strokes may be considered less severe than cortical strokes; however, scientific evidence for this is limited and based primarily on overall cognitive impairment. Thus, the aim was to scrutinize domain-specific differences between the groups.

In **Study II**, the aim was to assess the effects of executive dysfunction on memory performance. In a more homogenous patient group than in previous studies of similar design, the aim was to scrutinize comparatively well-defined executive dysfunction and verbal and visual memory performance profiles, while further controlling the effects of general reasoning ability.

In **Study III**, the aim was to examine domain-specific cognitive profiles and recovery post first-ever stroke in a working-aged cohort. The aim was twofold: first, to evaluate the domain-specific impairment rates and overall cognitive impairment rate from early states to chronic states post stroke, and second, to examine domain-specific cognitive change during the follow-up.

3 METHODS

3.1 PARTICIPANTS

Participants in the present **Studies I–III** were part of a consecutive cohort of working-aged first-ever ischemic stroke patients from two Finnish central hospitals, Helsinki University Hospital and Lapland Central Hospital. Intake was between June 2007 and October 2009. Inclusion criteria were first-ever diagnosed supratentorial infarction, working aged (18–65 years) and native Finnish speaker. Exclusion criteria were severely altered state of consciousness hindering cooperation markedly throughout the first weeks post stroke and medical history of neurological or psychiatric diseases known to affect cognition.

The initial intake was 230 patients. Before reaching this patient count, 19 patients were lost due to logistical reasons, such as rapid discharge to home or secondary care, and 38 patients due to refusal to participate. The first seven patients were not eligible for follow-ups more than 3 months post stroke due to study protocols and expanding study permissions.

According to the study protocol, neuropsychological examinations were conducted at baseline (a brief examination within the first weeks post stroke), and at 3 months, 6 months, 1 year (a subpopulation was examined) and 2 years after the initial stroke. In **Studies I–III**, baseline, 6-month and 2-year examinations were used. The neuropsychological baseline examinations were conducted when a clinical neurologist had deemed the patients sufficiently stable and ready to be discharged to either home or an active rehabilitation unit. Stability of patient status was sought to minimize possible biasing effects of fluctuating acute conditions (e.g., fatigue) in neuropsychological performance. Neurological examinations were conducted at baseline and at 6 months and 2 years after the initial stroke.

All patients were treated according to institutional guidelines and received standard stroke care. All patients underwent brain imaging for clinical purposes during the acute phase of the stroke (at baseline), and the clinical brain scans were brain computerized tomography (CT) and/or magnetic resonance imaging (MRI). MRI scans or baseline follow-up CT scans have been chosen for the present study when possible.

A demographically matched and healthy control group was gathered from patients' peers, friends and relatives. The control group comprised 50 persons. All control subjects met the inclusion and exclusion criteria set for patients, except for stroke history. The control group was examined twice, with a 3-month interval between the examinations.

All patients and control subjects provided written informed consent for participation. If initial consent was given by the patient's next of kin due to lowered understanding at the baseline, personal consent was requested at

follow-up examinations. The Ethics Committee of the Department of Medicine, Helsinki University Hospital, approved the study protocol and the consent procedure (register number 102/E9/07). All research procedures were completed in accordance with the Helsinki Declaration.

3.1.1 STUDY I SUBPOPULATION

In **Study I**, data from neuropsychological and neurological examinations at baseline and 6 months were used. Patients with unilateral brain infarction that visualized on brain imaging and was located in either cortical or subcortical areas but did not encompass gray matter in both were included in **Study I**. Thus, 51 patients with no visible lesions, seven patients with bilateral infarctions, and 36 patients with lesions covering both cortical and subcortical gray matter were excluded. In addition, four severely aphasic patients were excluded before the baseline examination, as they were not able to complete many of the neuropsychological tasks. This left 132 patients for the baseline study. In addition, before the 6-month examination, three patients had experienced recurrent brain damage (e.g., stroke, tumor) and were excluded, and 20 were lost to follow-up due to, for example, moving to another hospital district, refusal or loss of contact. This left 109 patients for the follow-up.

3.1.2 STUDY II SUBPOPULATION

In **Study II**, data from neuropsychological and neurological examinations at 6 months and 2 years were used. Seven patients with recurrent brain damage before the 6-month examination, 11 persistently severely aphasic patients at 6 months and one patient with severe depression that hampered motivation and effort in neuropsychological examination were excluded. Before 6 months, 25 patients were lost to follow-up. This left 179 patients for the 6-month examination. In addition, four patients with recurrent brain damage between the 6-month and 2-year examinations were excluded, three patients died before the 2-year mark and 27 patients were lost to follow-up between 6 months and 2 years, leaving 145 patients at 2 years.

To control for learning effects, patients' performance at follow-up examinations at 6 months and 2 years post stroke was compared with control subjects' performance during their second examination.

3.1.3 STUDY III SUBPOPULATION

In **Study III**, data from neuropsychological and neurological examinations at baseline, 6 months and 2 years were used. Thirteen patients who had recurrent brain damage and eight who died before the 2-year examination were excluded. Furthermore, 49 patients were lost to follow-up. This left 153 patients who participated in all three examinations for this sub-study.

Patients' performance at baseline was compared with control subjects' performance in the latter group's first examination, and patients' performance at follow-up examinations at 6 months and 2 years post stroke was compared with control subjects' performance in their second examination.

3.2 NEUROPSYCHOLOGICAL EXAMINATION

All neuropsychological examinations were performed according to a written research protocol. All examinations were one on one and performed in a quiet office setting.

Baseline brief examination included Logical Memory tests I and II (LM I and LM II) of the Wechsler Memory Scale – Revised (WMS-R; Wechsler, 1987; Wechsler, 1996), a list learning task of ten words with five learning trials and recalling the wordlist after a 30-min delay (Christensen, 1979), recalling geometric figures in odd-numbered tablets of the Revised Visual Retention Test (BRVRT) immediately and in Tablets 1 and 3 after delay (Benton, 1974), the backwards Digit Span task of the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Wechsler, 1997; Wechsler, 2005), a phonemic fluency task of producing as many words beginning with the letter K in one minute as possible (Lezak, Howieson, Bigler, & Tranel, 2012), the Trail Making test forms A and B (TM A and TM B; Reitan, 1958; see also Poutiainen, Kalska, Laasonen, Närhi, & Räsänen, 2010), a finger tapping task with a tapping device, a Visuospatial Searching task with four landscape orientation tablets where parallel lines are searched amidst a group of distracting lines of different orientations (Vilkki, 1989), drawing four visuospatial figures (triangle, flag, cube, 3D-cross; Lezak et al., 2012), the Token test (shortened version; De Renzi & Faglioni, 1978), the visual naming task (shortened version) of the Boston Diagnostic Aphasia Examination (BDAE; Goodglass & Kaplan, 1983; see also Laine, Niemi, Koivuselkä-Sallinen, & Tuomainen, 1997) and the repetition of a long sentence (Christensen, 1979).

All tests and tasks performed at baseline were repeated at 6 months. In addition, the 6-month examination included naming colors (form A) and naming the colors of incongruent words (form B) of the Stroop Color and Word Test (Lezak et al., 2012; Stroop, 1935), Nelson's (1976) version of the Wisconsin Card Sorting Test (WCST) and the Similarities, Information, Digit Symbol and Block Design subtests of the WAIS-III.

The 2-year examination was similar to that at 6 months, except that only one story from LM I and II was used, the WCST was not repeated due to marked learning effects (Lezak et al., 2012) and the Token test, the BDAE and repetition of a long sentence were only used for a minority of patients who had demonstrated impaired performance in the previous examination.

Mood state was assessed with Profile of Mood States (POMS; McNair & Lorr, 1964): at baseline with a compact ten-item version and at follow-ups with the full 38-item Finnish version.

3.2.1 NEUROPSYCHOLOGICAL DOMAINS AND DATA TRANSFORMATIONS IN STUDY I

In **Study I**, patients' performance was evaluated at baseline in four cognitive domains: verbal memory, executive functions, visuospatial function and psychomotor speed. The measures of these domains were repeated at 6 months, and the evaluation of verbal reasoning and non-verbal reasoning domains was added.

For *verbal memory*, sum score of five learning trials of the list learning task, LM I score and a delayed recall percentage score, computed as LM II score divided by LM I score, were used. For *executive functions,* score of digit span backwards, score of phonemic fluency and subtraction score of time of the TM B minus time of the TM A (TM B-A time) were used. For *visuospatial function,* separate scores were drawn for correctly identified parallel lines on the right and left sides of the Visuospatial Searching task tablets. For *psychomotor speed,* time of the TM A and right-hand tapping speed were used. *Verbal reasoning* included scores of the Similarities and Information subtests of the WAIS-III, and *non-verbal reasoning* included scores of the Digit Symbol and Block Design subtests.

3.2.2 NEUROPSYCHOLOGICAL DOMAINS AND DATA TRANSFORMATIONS IN STUDY II

In **Study II**, patients' *executive functioning* at 6 months post stroke was evaluated with five measures: score of digit span backwards, score of phonemic fluency, TM B-A time, Stroop form B minus form A time (Stroop B-A time) and the number of perseverative errors in the WCST.

The executive performance of the patients was compared with that of the control group. Patients' performance in each measure at 6 months was considered defective when their test scores fell below the 10^{th} percentile level of the control group. Patients were categorized as executively impaired when two or more of the five executive measures were considered defective. In an effort to stabilize patient data, the categorization of executively impaired and intact patients at 6 months post stroke was used when comparing patient performance on memory test at 6 months and at 2 years.

Patients' *memory* was evaluated both at the 6-month and 2-year examinations, and the memory test scores used to compare patient performance included the following: sum score of five learning trials of the list learning task, score of delayed recall of the wordlist, numbers of correctly drawn geometric figures in BRVRT immediately and after delay, and scores of immediate and delayed recall of the first story and the second story of the LM. The exception to this was that at 2 years, only one story was used.

Patients' *reasoning* was evaluated both at 6 months and at 2 years with scores of the Similarities, Information, Digit Symbol and Block Design subtests of the WAIS-III. Z-scores for each of these subtests were calculated from the control group's second examination data. These four Z-scores were

averaged, and this mean Z-score was used to control for effects of general intelligence.

3.2.3 NEUROPSYCHOLOGICAL DOMAINS AND DATA TRANSFORMATIONS IN STUDY III

In **Study III**, patients' baseline, 6-month and 2-year assessments were used. For *executive functions,* three measures were used: score of digit span backwards, score of phonemic fluency and TM B-A time. For *verbal memory,* four measures were used: sum score of five learning trials of the list learning task, score of delayed recall of the wordlist, LM I score and LM II score. Again, however, only one story was used at 2 years, and scores of immediate and delayed recall of the one LM story were used instead. For *visual memory,* two measures – numbers of correctly drawn geometric figures in BRVRT immediately and after delay – were used. Three measures were used for *psychomotor speed*: time of the TM A, right-hand tapping speed and left-hand tapping speed. *Visuospatial functions* were evaluated with three measures: time of drawing four visuospatial figures and separate scores for correctly identified lines on the right and left sides of the Visuospatial Searching task tablets. *Basic language functions* were assessed for all patients only at the baseline and at 6 months, with three measures: score of the Token test, score of the visual naming of the BDAE and score of the repetition of a long sentence. *Reasoning ability* was assessed at both 6 months and 2 years, with two measures: scores of the Similarities and Block Design subtests of the WAIS-III.

Patients' Z-scores in each measure were calculated from the control data. The patients' baseline data were normalized with the control group's first examination data, and the patients' follow-up data were normalized with the control group's second examination data. All Z-scores within a cognitive domain were averaged. If this domain-specific mean Z-score was more than -1.65 SD below the control group's domain average, patients' performance was considered impaired in that domain. Measures of *language functions* were not sufficiently normal and thus patients' language functions were considered impaired when at least two of the three measures used were below the 5^{th} percentile level of the control group, as the 5^{th} percentile level corresponds to -1.65 SD. Patients were considered cognitively impaired when at least one cognitive domain was considered impaired.

Change within each cognitive domain between neuropsychological examinations was evaluated with difference scores. The difference score between the baseline and 6-month evaluations was the subtraction score of 6-month domain-specific Z-score minus the baseline domain-specific Z-score. The difference score between the 6-month and 2-year examinations was calculated similarly. Furthermore, control group scores were normalized with their own scores, and control group difference scores in each cognitive domain

between first and second examination were calculated in an effort to compare patients' change with the control group's change.

3.3 CLINICAL AND NEUROLOGICAL EXAMINATION, MEDICAL RECORDS AND REGISTRY DATA

An experienced stroke neurologist evaluated the patients at baseline, at 6 months and at 2 years. Three neurological scales were used: the National Institutes of Health Stroke Scale (NIHSS; Brott et al., 1989; Goldstein, Bertels, & Davis, 1989) at baseline (both at stroke unit admission and discharge), and at follow-ups (at the time of the neuropsychological examinations), the modified Rankin Scale (mRS; van Swieten, Koudstaal, Visser, Schouten, & van Gijn, 1988) at follow-ups and the Barthel Index (Mahoney & Barthel, 1965) at baseline and follow-ups (at the time of the neuropsychological examination). The NIHSS scores were categorized as either intact (0 points), mild to moderate (1–6 points) or severe (7+ points), as in a previous study (DeGraba, Hallenbeck, Pettigrew, Dutka, & Kelly, 1999)

The characteristics of the brain infarction were evaluated visually from the non-contrast CT or fluid-attenuated inversion recovery (FLAIR) MRI axial images that had been taken for clinical purposes at baseline. Data recorded were stroke size (largest identified diameter in millimeters), side, location (cortical vs. subcortical), silent infarction and co-occurring white matter changes matching ratings 2–3 on a white matter changes scale (beginning confluence of lesions or diffuse involvement of the entire region; Wahlund et al., 2001).

For **Study I**, infarcts were categorized to stroke in cortical gray matter (including additional white matter) or stroke in subcortical gray and/or white matter. For **Study II**, infarct data on whether the lesioned area involved frontal cortex, parietal cortex, temporal cortex, occipital cortex, insular cortex, lenticular nucleus, caudate nucleus, thalamus, deep white matter or white matter (corona radiata or centrum semiovale) were used. These recorded stroke locations accorded with an atlas (Moeller & Reif, 2007). For **Study II**, pure frontal cortex versus other gray matter location ("frontal location") was calculated. For **Study III**, the categorization of the strokes' pathophysiological etiologies (with Trial of Org 10172 in Acute Stroke Treatment criteria, TOAST; Adams et al., 1993) was used.

Information from medical records was also collected. The diagnoses of atrial fibrillation and carotid stenosis over 50 % were used in **Study I** and **Study III**, diabetes mellitus, serum cholesterol levels and smoking habits in **Study III**, and large artery atherosclerotic infarction in **Study I**. For **Study III**, data on patients' alcohol consumption, working status and neuropsychological rehabilitation were also used. Alcohol consumption was evaluated with two questions (Alcohol Use Disorders Identification Test – QF; Aalto, Tuunanen, Sillanaukee, & Seppä, 2006). Patients' working status before

stroke and at 2 years was categorized to being either (a) in the able workforce (including employed and unemployed patients and students) or (b) retired (including patients on sick leave), based on Finnish Social Insurance Institution and Finnish Centre for Pensions registry data and an interview. Data on rehabilitation were gathered from medical records and interviews.

3.4 STATISTICAL ANALYSES

For statistical analyses, SPSS 16.0 and IBM SPSS Statistics 22 and 23 were used. To evaluate differences between demographical, radiological and neurological variables, Chi-square (χ^2) and Mann-Whitney U tests were used. Cognitive variables were analyzed with multivariate analysis of variance or covariance (MANOVA or MANCOVA) and subsequently with analysis of variance or covariance (ANOVA or ANCOVA). The variables controlled in covariance analysis were lesion size and hemisphere in **Study I**, age and general intelligence in **Study II** and age and education in **Study III**. Interaction terms between study variables and control variables were checked, and when not significant in MANCOVA, results were reported from models without these interaction terms. Square root transformations were used to obtain variable normality in analyses when needed, but untransformed means were reported to retain the understandability of results. Few test scores were imputed in **Study III**. In **Study I**, inferential confidence intervals (ICI; Tryon, 2001) were also computed for baseline variables. The statistical significance level was set at 0.05 in all studies. Multiple comparisons were corrected with the Benjamini-Hochberg correction (Benjamini & Hochberg, 1995) in **Study II** and with the Bonferroni correction in **Study III**'s pairwise post-hoc analyses. Partial eta squared (η_p^2) was used for estimate of effect sizes in **Study II** and **Study III**.

4 RESULTS

4.1 DEMOGRAPHICS

In **Studies I–III**, somewhat different subpopulations were used, due to differing supplementary exclusion criteria (e.g., inclusion of only visible lesions in restricted areas in **Study I**). The baseline examination results were used in **Study I** (132 patients were included at this timepoint) and **Study III** (n = 153), 6-month results in **Studies I–III** (**Study I**: n = 109; **Study II**: n = 179; **Study III**: n = 153) and 2-year results in **Study II** (n = 145) and **Study III** (n = 153).

Differences in subpopulation demographics were minimal. Patients were, on average, 54.0–54.4 years (range 18–66 years) at the examination first used in each study and possessed a mean of 12.0–12.3 years of education (range 9–20 years); 59.8–68.2 % were men, and they were neuropsychologically assessed, on average, 8.1–8.2 days (range 2–30 days), 6.1–6.2 months (range 3.7–8.4 months) and 24.3 months (range 22.8–26.5 months) post stroke.

Control group participants were, on average, 54.3 years (range 23–65) at their first examination and possessed a mean of 12.4 years of education (range 9–20); 62.0 % were men. The patients' demographics did not differ from those of the control group's ($p > .2$ in all cases).

Different numbers of patients were excluded from **Studies I–III**, and those patients' profiles were studied. In **Study III,** 21 patients initially included in the cohort were excluded, and 49 dropped out before the 2-year examination; these non-included patients were less educated ($p = .010$), more likely consumed alcohol substantially ($p = .001$) and were more likely impaired in psychomotor speed ($p = .038$) and executive functions ($p = .048$) than the included 153 patients. Furthermore, 62.9 % of the patients not included to **Study III** were categorized as cognitively impaired at baseline, compared with 49.0 % of the included patients ($\chi^2 = 3.695$; $p = .055$). The non-included and included patients did not differ significantly in other demographical, stroke or clinical characteristics, risk factors, baseline mood or working status before stroke in **Study III**. In **Study II,** 19 initially included patients were excluded, and 25 dropped out, before the 6-month examination; these non-included patients were more likely to be men and possessed less education, worse initial neurological deficits and larger strokes that involved more brain areas than the included 179 patients ($p < .05$ in all cases). The non-included and included patients did not differ significantly, however, in age, stroke side, subcortical–cortical location or frequency of vascular degeneration in **Study II**. In **Study I**, in addition to excluding patients due to the critical stroke location exclusion criteria, only four patients with severe aphasia were excluded, and demographic comparisons between these four excluded and the 132 included patients were not feasible.

During the follow-ups, 23 patients dropped out between baseline and 6 months in **Study I** – 109 were re-evaluated – and 34 patients dropped out between 6 months and 2 years in **Study II** – 145 were re-evaluated. The drop-outs did not differ in demographical, neurological or clinical variables or cognitive domains from the re-evaluated patients, except in white matter changes (**Study I**), which were more pronounced in the drop-outs than the re-evaluated patients ($p = 0.045$), as well as age and general intelligence (**Study II**), as the drop-outs were younger ($p = .026$) and had lower general intelligence scores at 6 months ($p = .019$). In **Study III**, the same 153 patients were examined throughout the study.

4.2 COMPARISON OF SUBCORTICAL AND CORTICAL STROKES (STUDY I)

Of the 132 patients included at baseline, 71 had subcortical strokes, and 61 had cortical strokes. In terms of demographic and clinical variables, the groups differed only in lesion size, as subcortical strokes were, on average, smaller than cortical strokes ($p < .001$). This was thus controlled for in further analyses, in addition to controlling for stroke side. The patient groups did not differ in, for example, mood states or NIHSS scores.

Patients with subcortical strokes performed inferiorly to patients with cortical strokes in the verbal memory domain (MANCOVA, $F_{3,126} = 4.187$, $p = .007$) and in the psychomotor speed domain (MANCOVA, $F_{2,118} = 3.302$, $p = .040$). In terms of the individual tasks, patients with subcortical strokes were significantly inferior to patients with cortical strokes in one of the three verbal memory tasks – delayed recall percentage (65.89 ± 2.59, mean ± standard error of the mean, SEM vs. 76.86 ± 2.84 ANCOVA, $F_{1,128} = 8.308$, $p = .005$) – and both psychomotor speed tasks – time of the TM A (60.95 ± 3.54, mean ± SEM vs. 49.72 ± 3.94 ANCOVA, $F_{1,119} = 4.324$, $p = .040$) and right-hand tapping speed (43.54 ± 1.38, mean ± SEM vs. 48.22 ± 1.53 ANCOVA, $F_{1,119} = 3.985$, $p = .048$). No differences were found between patients with subcortical and cortical strokes in the domains of executive functions or visuospatial function. In addition, with Inferential Confidence Intervals (ICI), equivalence in the performance between patients with subcortical and cortical strokes was confirmed in two of the three executive function tasks (namely, phonemic fluency and digit span backwards, but not TM B-A time), as well as in one verbal memory task (LM I) and one visuospatial function task (right side search).

The strokes were confirmed and assessed by CT (70 patients; 53.0 %) or MRI (62 patients; 47.0 %), on average, 2.7 days post stroke (range 0–22, except for one patient assessed after 143 days).

All patients included at 6 months ($n = 109$) were well recovered, as measured with the neurological scales used at 6 months: Barthel Index (98.2 % had an intact score), NIHSS (63.8 % of patients with subcortical

strokes and 49.0 % of patients with cortical strokes had intact scores; the remainder had scores indicating mild to moderate impairment; p = 0.120) and modified Rankin Scale (97.2 % with a maximum score of 2). Patients with subcortical strokes did not differ significantly from those with cortical strokes in terms of mood state.

At the 6-month follow-up, patients with subcortical strokes and patients with cortical strokes did not differ significantly from each other in any of the measured cognitive domains: verbal memory, executive functions, visuospatial function, psychomotor speed, verbal reasoning or non-verbal reasoning. Yet, out of the individual tasks, patients with subcortical strokes still performed inferiorly to patients with cortical strokes in delayed recall percentage (78.44 ± 2.11, mean ± SEM vs. 85.86 ± 2.29; ANCOVA, $F_{1,105} = 5.307$, p = .023). Adjusting the two groups for baseline scores did not reveal any significant between-group differences in the recovery of cognitive functions.

4.3 ASSOCIATIONS OF EXECUTIVE DYSFUNCTION AND MEMORY PROBLEMS (STUDY II)

Of the 179 patients included at 6 months, 32.6 % were impaired in Stroop B-A time, 30.7 % in TM B-A time, 27.9 % in WCST (perseverative errors), 17.9 % in phonemic fluency and 17.9 % in WAIS-III digit span backwards. Those 66 patients (36.9 %) who had impaired scores in at least two of these measures were classified as executively impaired. Demographic comparisons between the executively impaired (n = 66) and intact (n = 113) patients are shown in **Table 1**. Executively impaired patients had lower general intelligence scores, were older and were less educated than executively intact patients (p < .001 in all cases), but the difference in education was no longer significant after controlling for age and general intelligence score (p = .208). Therefore, general intelligence and age, but not education, were controlled for in further analyses.

Table 1 *Demographical, neurological and clinical characteristics of patients who were executively impaired and intact 6 months post stroke.*

Characteristics	Executively impaired[a] N = 66	Executively intact N = 113	*p*
Gender, men (*N*)	44 (66.7 %)	63 (55.8 %)	0.151
Age, years, mean (*M*)	59.1 (SD = 5.1)	51.3 (SD = 11.3)	< 0.001
Education, years (*M*)	10.8 (SD = 2.1)	13.0 (SD = 2.7)	< 0.001
White matter changes[b] (*N*)	10 (15.2 %)	15 (13.4 %)	0.744
Silent infarctions[b] (*N*)	18 (27.3 %)	23 (20.5 %)	0.302
Stroke size[b],	26.5 (SD = 28.0)	18.7 (SD = 20.9)	0.146

largest diameter in mm (*M*)			
Stroke side[b] (*N*)			0.218
non-visible	18 (27.3 %)	24 (21.4 %)	
right	22 (33.3 %)	43 (38.4 %)	
left	25 (37.9 %)	36 (32.1 %)	
bilateral	1 (1.5 %)	9 (8.0 %)	
Stroke location[b] (*N*)			0.529
non-visible	18 (27.3 %)	24 (21.4 %)	
cortical	23 (34.8 %)	33 (29.5 %)	
subcortical	17 (25.8 %)	39 (34.8 %)	
cortico-subcortical	8 (12.1 %)	16 (14.3 %)	
Stroke location[b] (*N*)			0.787
non-visible	18 (27.3 %)	24 (21.4 %)	
pure frontal cortex	1 (1.5 %)	1 (0.9 %)	
other than frontal cortex	39 (59.1 %)	74 (66.1 %)	
frontal cortex and other gray areas	8 (12.1 %)	13 (11.6 %)	
Stroke involvement of[b] (*N*)			
Frontal cortex	9 (13.6 %)	14 (12.5 %)	0.827
Parietal cortex	18 (27.2 %)	25 (22.3 %)	0.456
Temporal cortex	15 (22.7 %)	22 (19.6 %)	0.624
Occipital cortex	11 (16.7 %)	24 (21.4 %)	0.440
Insular cortex	9 (13.6 %)	9 (8.0 %)	0.231
Lenticular nucleus	10 (15.2 %)	14 (12.5 %)	0.617
Thalamus	6 (9.1 %)	27 (24.1 %)	0.013
Caudate nucleus	4 (6.1 %)	8 (7.1 %)	0.781
Deep white matter	14 (21.2 %)	22 (19.6 %)	0.801
White matter	22 (33.3 %)	33 (29.5 %)	0.589
NIHSS[c] impaired, 1–6 points (*N*)	34 (51.5 %)	46 (40.7 %)	0.161
mRS[d] impaired, 1–4 points (*N*)	46 (69.7 %)	67 (59.3 %)	0.164
Barthel Index[e] impaired, 55–95 points (*N*)	2 (3.0 %)	3 (2.7 %)	0.883
Visual naming (BDAE[f], shortened version) impaired, 77–90 points out of 93 (*N*)	15 (22.7 %)	16 (14.2 %)	0.144
Mood State (full modified POMS[g]), sum score (M)	42.5 (SD = 26.8)	37.0 (SD = 23.9)	0.218
General Intelligence[h], Z-score (*M*)	-1.15 (SD = 0.70)	-0.01 (SD = 0.78)	< 0.001

Chi-square (χ^2; in data with numbers, *N*) and Mann-Whitney U (in data with means, *M*) tests were used. Gender, education and brain imaging data collected at baseline; other data collected at 6 months. [a]At minimum, two executive measures defective out of five measures used at 6-month neuropsychological examination. [b]N = 178 in brain imaging. [c]National Institutes of Health Stroke Scale (Brott et al., 1989; Goldstein et al., 1989). [d]Modified Rankin Scale (van Swieten et al., 1988). [e](Mahoney & Barthel, 1965). [f]Boston Diagnostic Aphasia Examination (Goodglass & Kaplan, 1983; Laine et al., 1997). [g]Profile of Mood States (McNair & Lorr, 1964); N = 165. [h]Wechsler Adult intelligence Scale – Third Edition (WAIS-III; Wechsler, 1997; Wechsler, 2005), average of Similarities, Information, Digit Symbol and Block Design.

With the 6-month data, MANCOVA for executively impaired versus intact patients on memory variables controlling for general intelligence and age showed a significant main effect ($F_{8,168} = 2.704$; $p = .008$; $\eta_p^2 = 0.114$). In further ANCOVAs for individual memory variables, executively impaired patients performed inferiorly to executively intact patients in the list learning task ($p = .001$) and the immediate recall of the first story of the LM ($p = .010$), as seen in **Table 2.** When not controlling for general intelligence or age, executively impaired patients performed inferiorly to executively intact patients in all memory tasks.

At 2 years, of the 145 patients remaining in the study, 53 were executively impaired, and 92 executively intact, as classified at the 6-month examination. No new demographical, neurological or clinical differences emerged between the groups: executively impaired patients still demonstrated lower general intelligence measured at 2 years and were older and less educated.

With the 2-year memory and demographic data, MANCOVA for executively impaired versus intact patients on memory variables controlling for general intelligence and age showed a significant main effect ($F_{6,136} = 3.695$; $p = .002$; $\eta_p^2 = 0.140$). In further ANCOVAs for individual memory variables, executively impaired patients (classified at the 6-month examination) performed inferiorly to executively intact patients in list learning task ($p < .001$), delayed recall of the wordlist ($p = .006$), and in immediate recall of geometric figures in BRVRT ($p = .007$), **Table 2.**

Furthermore, frequency of executive impairment was calculated at 2 years. The WCST was not repeated and thus only four executive measures were used. Forty-one patients (28.3 %) had at least two defective scores in these at 2 years and were classified as executively impaired. Even with different classification criteria for executive impairment at 6 months and at 2 years, 83.4 % ($n = 121$) of patients were consistently classified as executively intact or impaired at both examinations. When using the 2-year executive impairment classification, 2-year memory results were similar to the results reported previously, except that the group difference in list delayed recall did not reach significance after the statistical correction (Benjamini & Hochberg, 1995).

Table 2 *Demographical, neurological and clinical characteristics of patients who were executively impaired and intact 6 months post stroke.*

Memory measures, mean ± SEM	**6 months**				**2 years**			
	Executively impaired[a] N = 66	**Executively intact N = 113**	***p***	**η_p^2**	**Executively Impaired[a] N = 53**	**Executively Intact N = 92**	***p***	**η_p^2**
List learning task[b]	37.68 ± 0.77	41.66 ± 0.55	0.001[c]	0.058	38.35 ± 0.87	43.26 ± 0.62	0.000[c]	0.096
Delayed recall of the wordlist[b]	7.10 ± 0.33	7.47 ± 0.24	0.275	0.007	7.07 ± 0.33	8.27 ± 0.23	0.006[c]	0.052
Immediate recall of the first story of the LM[d]	11.85 ± 0.53	13.73 ± 0.38	0.010[c]	0.037	13.65 ± 0.58	14.47 ± 0.41	0.304	0.008
Delayed recall of the first story of the LM[d]	9.53 ± 0.54	10.83 ± 0.39	0.077	0.018	11.72 ± 0.58	12.69 ± 0.41	0.220	0.011
Immediate recall of the second story of the LM[d]	13.23 ± 0.56	13.97 ± 0.40	0.330	0.005				
Delayed recall of the second story of the LM[d]	11.99 ± 0.59	12.23 ± 0.43	0.766	0.001				
Immediate recall of geometric figures in BRVRT[e]	10.21 ± 0.23	10.73 ± 0.17	0.131	0.013	10.34 ± 0.24	11.16 ± 0.17	0.007[c]	0.050
Delayed recall of geometric figures in BRVRT[e]	2.82 ± 0.18	2.78 ± 0.13	0.969	0.000	3.02 ± 0.22	2.67 ± 0.15	0.294	0.008

Analysis of covariance (ANCOVA) controlling for patients' age and general intelligence (average of Similarities, Information, Digit Symbol and Block Design of the Wechsler Adult intelligence Scale – Third Edition (WAIS-III; Wechsler, 1997; Wechsler, 2005)). [a]At minimum, two executive measures defective out of five measures used at 6-month neuropsychological examination. [b]From (Christensen, 1979), list learning task with sum score of five learning trials. [c]Significant after adjusting by Benjamini-Hochberg correction (Benjamini & Hochberg, 1995). [d]Logical Memory test of the Wechsler Memory Scale – Revised (WMS-R; Wechsler, 1987; Wechsler, 1996). [e]Benton Revised Visual Retention Test (Benton, 1974), number of correctly drawn geometric figures in odd-numbered tablets immediately, and in Tablets 1 and 3 after delay.

4.4 RECOVERY OF DOMAIN-SPECIFIC COGNITIVE FUNCTIONING IN 2-YEAR FOLLOW-UP (STUDY III)

With 153 patients included, domain-specific impairment was most common in psychomotor speed throughout **Study III**, followed by impairment in executive functions. For the impairment rates of domain-specific cognitive functions, see **Figure 1**. The largest decrease in impairment rates occurred in visual memory, and the longest trajectory of recovery in psychomotor speed. Taken together, 49 % (n = 75) of patients were impaired in at least one domain at baseline, 41 % (n = 63) at 6 months and 39 % (n = 60) at 2 years. In most patients (90 %), this cognitive status did not change between 6 months and 2 years (that is, patients were consistently either impaired or intact at both time points).

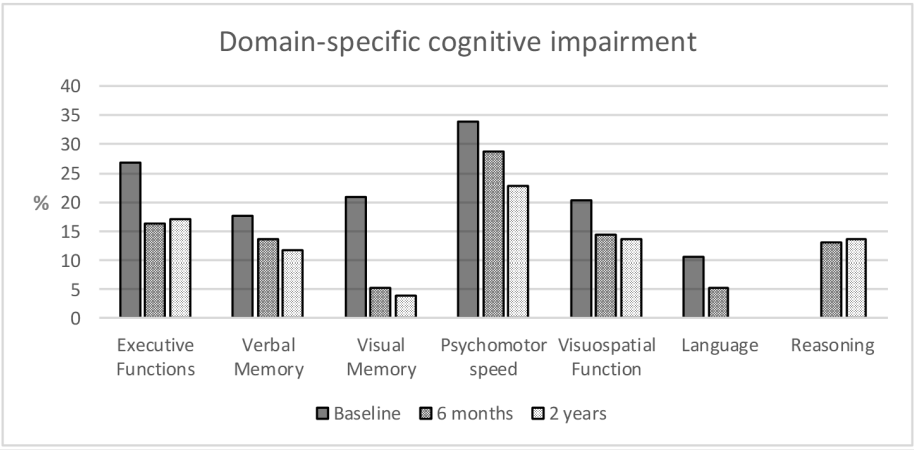

Figure 1 Percentage of patients impaired in cognitive domains at baseline, at 6 months and at 2 years post stroke. Impairment was defined as average performance in each cognitive domain, with Z < -1.65, in comparison with data from healthy control participants; patients' baseline data were normalized with the control group's first examination data; patients' follow-up data were normalized with the control group's second examination data.

Patients who were categorized as cognitively impaired at baseline, 6 months or 2 years were older and less educated than patients categorized as cognitively intact at the same time points ($p < .001$ in all cases), and they also experienced more neurologically severe strokes (e.g., NIHSS scores, $p < .05$), see **Table 3**. At baseline, cognitively impaired patients also suffered larger strokes ($p < .001$), but cognitively impaired and intact patients did not differ in gender, stroke risk factors, stroke side, etiology or the occurrence of coinciding brain chances. Cognitively impaired and intact patients at baseline

did not differ in mood state (POMS scores), but patients categorized as cognitively impaired at 6 months or 2 years demonstrated lower moods compared with cognitively intact patients at the same time points ($p < .05$ in all cases), as seen in **Table 3**. The numbers of patients with impaired neurological scores (e.g., NIHSS or mRS) decreased throughout the follow-up period, yet many patients who were categorized as cognitively impaired had normal scores in NIHSS (n = 12 at baseline, n = 20 at 6 months and n = 33 at 2 years) or excellent scores in mRS (i.e., ≤ 1; n = 25 at 6 months and n = 35 at 2 years). At baseline, no significant differences in working status existed between cognitively impaired or intact patients. The patients who were in the able workforce before the stroke and were cognitively impaired at 2 years were more likely to be retired or on sick leave than patients who were cognitively intact at 2 years (**Table 3**). One-fourth of the patients (n = 39) received neuropsychological rehabilitation, which begun prior to 6 months post stroke for 36 patients and lasted beyond 6 months post stroke for 32 patients. Patients who were categorized as cognitively impaired at baseline received more neuropsychological rehabilitation than cognitively intact patients ($p < .001$). However, patients who were categorized as cognitively impaired or intact at 6 months did not differ in neuropsychological rehabilitation received after 6 months post stroke.

Table 3 *Demographical and clinical characteristics of patients who were cognitively impaired and intact at baseline, at 6 months and at 2 years post stroke.*

	Baseline			**6 months**			**2 years**		
	Cognitively Impaired[a] N = 75	**Cognitively Intact N = 78**	**p**	**Cognitively impaired[a] N = 63**	**Cognitively Intact N = 90**	**p**	**Cognitively impaired[a] N = 60**	**Cognitively intact N = 93**	**p**
Demographics									
Gender, men *(N)*	49 (65.3 %)	49 (62.8 %)	0.746	39 (61.9 %)	59 (65.6 %)	0.643	36 (60.0 %)	62 (66.7 %)	0.401
Age, years, mean *(M)*	56.8 (SD = 9.3)	52.1 (SD = 9.9)	< 0.001	59.1 (SD = 6.3)	52.0 (SD = 10.9)	< 0.001	60.4 (SD = 6.4)	53.9 (SD = 10.8)	< 0.001
Education, years, *(M)*	11.6 (SD = 2.5)	12.9 (SD = 2.7)	< 0.001	11.4 (SD = 2.8)	12.9 (SD = 2.4)	< 0.001	11.0 (SD = 2.2)	13.1 (SD = 2.7)	< 0.001
Clinical characteristics									
NIHSS[c], admission *(N)*			0.035						
normal	6 (8.0 %)	8 (10.3 %)							
1–6 points	52 (69.3 %)	64 (82.1 %)							
7 or more points	17 (22.7 %)	6 (7.7 %)							
NIHSS[c], discharge/follow-up *(N)*			< 0.001			< 0.001			0.189
normal	12 (16.0 %)	37 (47.4 %)		20 (31.7 %)	57 (63.3 %)		33 (55.0 %)	62 (66.7 %)	
1–6 points	55 (73.3 %)	41 (52.6 %)		40 (63.5 %)	33 (36.7 %)		26 (43.3 %)	31 (33.3 %)	
7 or more points	8 (10.7 %)	0		3 (4.8 %)	0		1 (1.7 %)	0	
mRS[d] impaired, 2–4 points *(N)*				38 (60.3 %)	25 (27.8 %)	0.001	25 (41.7 %)	12 (12.9 %)	< 0.001
Barthel Index[e] impaired, 25–95 points *(N)*	35 (46.7 %)	7 (9.0 %)	< 0.001	5 (7.9 %)	1 (1.1 %)	0.032	5 (8.3 %)	1 (1.1 %)	0.024

Mood State (compact modified POMS)[f], sum score *(M)*	13.9 (SD = 6.4)	12.2 (SD = 5.8)	0.098	14.8 (SD = 7.6)	10.3 (SD = 7.0)	< 0.001	13.5 (SD = 7.5)	11.0 (SD = 7.1)	0.041
Mood State (full modified POMS)[f], sum score *(M)*				51.2 (SD = 27.7)	34.0 (SD = 24.0)	< 0.001	48.1 (SD = 29.0)	36.2 (SD = 23.7)	0.018
Working status[g]									
Status before stroke			0.785	Status before stroke – at 2 years					< 0.001
workforce	60 (80.0 %)	61 (78.2 %)		workforce – workforce			6 (10.2 %)	55 (59.1 %)	
				workforce – retired			37 (62.7 %)	22 (23.7 %)	
retired	15 (20.0 %)	17 (21.8 %)		retired – retired			16 (27.1 %)	16 (17.2 %)	

[a]At minimum, one cognitive domain impaired. [b]N = 152 in high serum cholesterol, smoking and brain imaging. [c]National Institutes of Health Stroke Scale (Brott et al., 1989; Goldstein et al., 1989). [d]Modified Rankin Scale (van Swieten et al., 1988). [e](Mahoney & Barthel, 1965) [f]Profile of Mood States (McNair & Lorr, 1964); N = 144 at baseline, N = 146 at 6 months, and N = 145 at 2 years. [g]Workforce category includes employed and unemployed patients and students; retired category includes patients on sick leave; N = 152 at 2 years.

To study how domain-specific cognitive performance changed between the baseline and 6 months, those patients who were cognitively impaired in any domain at baseline (n = 75) were compared with cognitively intact patients (n = 78) and the control group (n = 50). Domain-specific difference scores between baseline and 6 months (i.e., 6-month mean Z-score minus baseline mean Z-score) differed between the three groups (MANOVA; $F_{10,392} = 8.464$; $p < .001$; $\eta_p^2 = .178$; Wilks' lambda = 0.676). Further ANOVAs showed the difference to be significant for verbal memory ($p = .016$; $\eta_p^2 = 0.040$), as well as all other domains ($p < .001$ in all cases; $\eta_p^2 = 0.076–0.189$). The mean difference scores between baseline and 6 months in each cognitive domain are shown in **Figure 2**. Post-hoc analyses (pairwise Bonferroni) demonstrated that cognitively impaired patients improved more than cognitively intact patients in all cognitive domains ($p < .01$), except for verbal memory ($p = .130$), and more than the control group in all cognitive domains (verbal memory $p = .019$, others $p \leq .001$). In visual memory performance, even patients categorized as cognitively intact at baseline improved more than the control group ($p = .001$). When controlling for age and education, cognitively impaired patients improved more than cognitively intact patients ($p < .01$) and the control group ($p < .01$) in verbal memory, as well as in all other domains.

To study how domain-specific cognitive performance changed between 6 months and 2 years, the patients who were cognitively impaired in any domain at 6 months (n = 63) were compared with cognitively intact patients (n = 90). Domain-specific difference scores between 6 months and 2 years (i.e., 2-year mean Z-score minus 6-month mean Z-score) did not differ significantly between the two groups (MANOVA $F_{6,146} = 1.025$; $p = .411$; $\eta_p^2 = 0.040$; $p > .05$ in all ANOVAs). **Figure 3** shows the mean difference scores in each cognitive domain. When controlling for age and education, these results did not change.

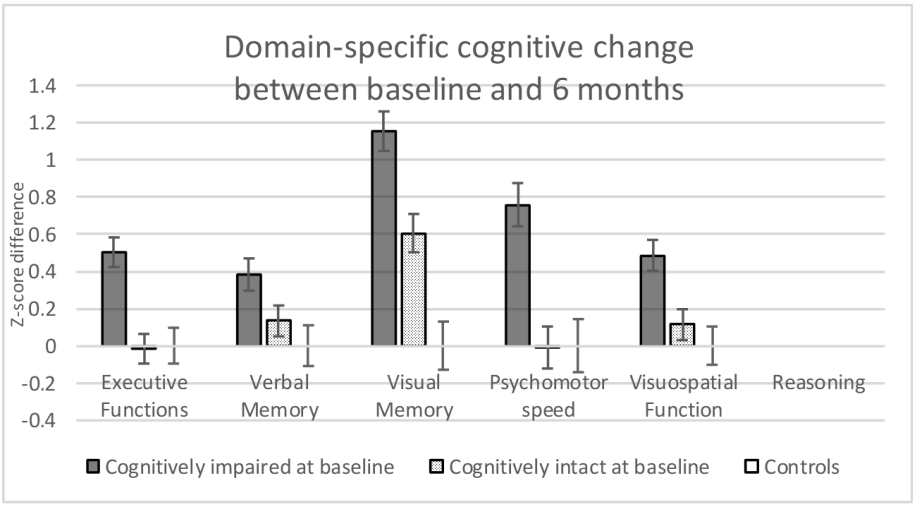

Figure 2 Mean difference scores within cognitive domains (error bars indicate ± SEM). Difference score indicating change is the subtraction score of 6-month follow-up domain-specific averaged Z-score minus baseline domain-specific averaged Z-score. The patients' baseline data and the control group's first examination data were normalized with the control group's first examination data. The patients' 6-month follow-up data and the control group's second examination data were normalized with the control group's second examination data.

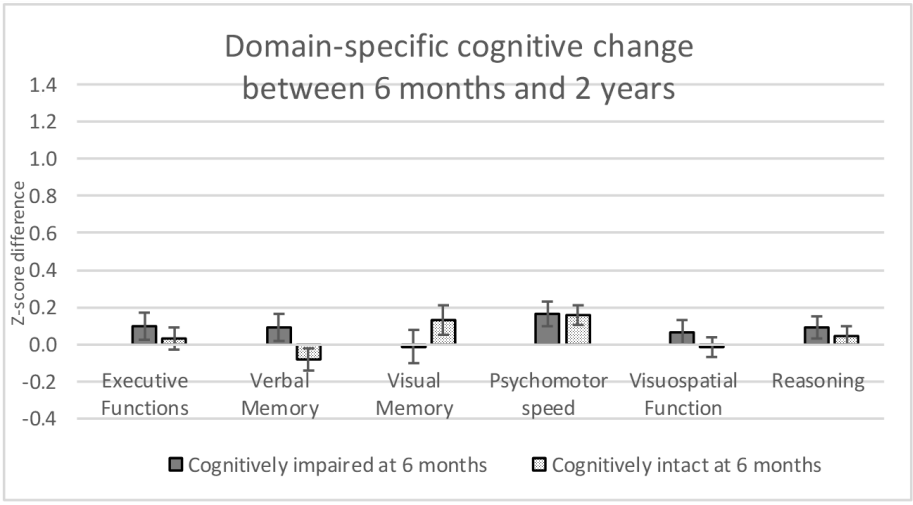

Figure 3 Mean difference scores within cognitive domains (error bars indicate ± SEM). Difference score indicating change is the subtraction score of 2-year follow-up domain-specific averaged Z-score minus 6-month follow-up domain-specific averaged Z-score. The patients' 6-month and 2-year follow-up data were normalized with the control group's second examination data.

5 DISCUSSION

Studies I–III of the present thesis aimed to clarify the roles of cognitive dysfunction and, specifically, executive dysfunction and memory problems post stroke. In the studied working-aged first-ever stroke cohort, overall cognitive impairment was common: about half of the patients were cognitively impaired at baseline, and about two in five remained so both at 6 months and at 2 years post stroke. The patients were quite well recovered neurologically, and detailed neuropsychological assessments were needed to uncover cognitive impairment.

Executive functions and memory were both commonly impaired cognitive domains; only psychomotor speed was more likely to be impaired post stroke. Cognitively impaired patients showed recovery in all cognitive domains between the baseline and 6 months, but little after that. Executive impairment and memory problems were associated, as executively impaired patients performed worse than executively intact patients in those memory tasks that required the better use of active memory strategies. No specific locations of stroke – for example, subcortical or cortical strokes, strokes in either hemisphere or strokes involving frontal areas – related to executive impairment. Subcortical strokes, however, were found to be associated with impaired verbal memory performance, specifically delayed recall, and further with impaired psychomotor speed.

5.1 OVERALL COGNITIVE IMPAIRMENT, MOOD AND RETURN TO WORK AFTER STROKE

About half of patients were cognitively impaired, according to detailed neuropsychological assessment, early post stroke, and about two in five remained so both at 6 months and at 2 years post stroke (**Study III**). The first-ever stroke cohort examined was relatively young, and it is important to examine this patient group in detail, since the socio-economic burden of, for example, lost working years is high. The baseline cognitive impairment rate aligns with a previous sample that defined cognitive impairment similarly (Nys et al., 2007). The follow-up impairment rate in **Study III** conforms quite closely with other studies that have reported similar impairment rates at five and ten or more years post stroke, as up to approximately half of the patients performed below average, and about one-third were found to be impaired in different domains, although overall impairment rates were not provided (Barker-Collo et al., 2010; Schaapsmeerders et al., 2013). Higher cognitive impairment rates at both the baseline and later follow-ups have been shown in studies where single test scores or other less stringent criteria to denote

impairment have been used, where patients with recurrent strokes were also included or where patients were markedly older (Hurford et al., 2013; Jaillard et al., 2009; Middleton et al., 2014; Pinter et al., 2019; Rasquin, Lodder et al., 2004). In the present stroke cohort, all clinically diagnosed first-ever strokes were included, in contrast with some previous studies that included only patients with lesions visualized in brain imaging (Jaillard et al., 2009; Nys et al., 2007), which may lower the impairment rate found in **Study III** as well.

Cognitively impaired patients' performance improved more in all cognitive domains between baseline and 6 months post stroke when compared with either healthy control groups or cognitively intact patients (**Study III**), which closely corresponds well to previous findings (Nys, van Zandvoort, de Kort, Jansen, van der Worp et al., 2005). The cognitive status of the majority of patients, 90 %, was stable between 6 months and 2 years, and no significant domain-specific improvement was found between cognitively intact and impaired patients during this later follow-up period (**Study III**). A previous study suggests that performance in individual tests remains stable between 6 and 12 months in the majority of patients (Rasquin, Lodder et al., 2004), and one recent study with a small number of patients showed that patients' performance remains stable in most neuropsychological tasks between 7 months and 10 years post stroke (Elgh & Hu, 2019).

At baseline, cognitively impaired and intact patients' own estimations of mood state did not differ significantly (**Study III**). However, at 6 months and at 2 years post stroke, cognitively impaired patients' estimations of mood were lower than those of cognitively intact patients (**Study III**). Early cognitive impairment predicts later depressive symptoms (Nys et al., 2006), and, furthermore, depression (Kauhanen et al., 1999; Nakling et al., 2017) and fatigue (Pihlaja, Uimonen, Mustanoja, Tatlisumak, & Poutiainen, 2014) later post stroke correlate with cognitive impairments. The current results indirectly support the possibility of stroke-related cognitive impairments causing the observed lowered mood state. In a recent review, cognitive impairment was listed as a consistent predictor of post-stroke depression (Towfighi et al., 2017). Association between post-stroke cognitive impairments and lower mood places an emphasis on the importance of always assessing and providing appropriate treatment for mood problems post stroke. Also, similar mood states were reported in patients with subcortical or cortical strokes (**Study I**), as well as in patients who were executively impaired or intact (**Study II**), which further highlights the need to observe mood status in all patient groups.

The majority of patients – up to three out of four – had recovered clinically well by 2 years, as measured with NIHSS or mRS (**Study III**). However, many of these patients were found to be cognitively impaired in thorough neuropsychological assessment – altogether, nearly one-fourth of all patients in this working-aged group were clinically well recovered but cognitively impaired (**Study III**). This aligns with a growing body of evidence suggesting that the scores of neurological screening methods are not sufficient in

evaluating patients' cognitive performance post stroke, particularly so if mild to moderate deficits are considered (Bour et al., 2010; Hurford et al., 2013; Jokinen et al., 2015; Kauranen et al., 2014; Nakling et al., 2017; Nys, van Zandvoort, de Kort, Jansen, Kappelle, & de Haan, 2005). Executively impaired and intact patients did not differ in neurological or neuroradiological evaluations (**Study II**). Taken together, thorough neuropsychological assessments are needed to assess cognitive impairment, instead of more coarse neurological evaluations, particularly among the working aged.

As physical recovery alone does not suffice in the working life, physically well-recovered patients may not be able to return to their former occupations because of cognitive impairments (Gottesman & Hillis, 2010). In a previous study on the same cohort as in the current study, about two patients out of five who were working before stroke had returned to work by 6 months (Kauranen et al., 2013). The current study of cognitive recovery demonstrated that half of the patients who were in the able workforce before stroke had returned, at least part time, to the able workforce by 2 years (**Study III**). Criteria for working differed in these studies, and some patients may also have returned to work after 6 months, as returning to work increases with time (Edwards et al., 2018). Patients who were cognitively impaired at 2 years had more likely left the able workforce than cognitively intact patients by 2 years (**Study III**). In the previous study with the same patient cohort, it was found that the number of cognitive impairments early post stroke best predicted returning to work (Kauranen et al., 2013). Furthermore, a recent review noted that cognitive impairments were among the most common predictors of return to work (Edwards et al., 2018). Detailed cognitive assessments are, thus, again stressed, as they are important in predicting return to work.

5.2 EXECUTIVE DYSFUNCTION AFTER STROKE

Executive dysfunction was the second most affected cognitive domain post first-ever stroke in this cohort (**Study III**). At baseline, about one in four patients were considered to possess impaired executive functioning (**Study III**). In previous studies, first-ever stroke patients were impaired in the domain of executive functions or related tasks from between two out of five to half of cases early post stroke (Jaillard et al., 2009; Nys et al., 2007; Pinter et al., 2019; Rasquin et al., 2002). As mentioned above, the patient group in the current study included patients without visible lesions and was limited to working-aged stroke patients, which can explain a portion of the identified differences.

The decrease in impairment rate in executive function – 11 percentage points between baseline and 6 months – was the second largest next to that in visual memory (**Study III**). Some recovery of executive functioning has been consistently shown in studies from early post stroke (Hurford et al., 2013; Nys, van Zandvoort, de Kort, Jansen, van der Worp et al., 2005; Pinter et al., 2019).

From subacute state on, the evidence of executive recovery is indecisive (Hochstenbach et al., 2003; Sachdev, Brodaty, Valenzuela, Lorenz, & Koschera, 2004).

Executive dysfunction seemed to remain fairly stable beyond 6 months post stroke (**Studies II** and **III**). Impairment rate of executive dysfunction did not markedly change between 6 months and 2 years, when classification method was consistent (**Study III**). Furthermore, the majority of patients, 83 %, remained in the same executive impairment class (either impaired or intact) at both the 6-month and 2-year assessments, even when the classification was made with five measures at 6 months and four measures at 2 years (**Study II**). No previous study was found that inspected domain-specific recovery from 6 months on post stroke. In individual executive tasks, in line with the current findings, most patients' performance has been found to be stable after 6 months post stroke (Elgh & Hu, 2019; Rasquin, Lodder et al., 2004).

In **Study II**, the rates of executive impairment were higher than in **Study III**. Different criteria – for example, 10th and 5th percentile cut-off levels and three to five executive measures – were used to denote impairment in **Studies II** and **III**. In **Study III**, the three executive measures used were chosen because they were used throughout the study protocol, and in **Study II**, when inspecting executive dysfunction in more detail, all five possible measures were chosen. These different criteria may explain the differences between **Studies II** and **III**, as well as the differences identified when compared with previous studies with the same patient cohort (Kauranen et al., 2015), and others (e.g., Jaillard et al., 2010). Irrespective of the method used to calculate impairment rates, the executive impairment found did not seem to alleviate markedly beyond 6 months post stroke (**Studies II** and **III**).

Long-lasting executive impairment was still observed at 2 years, in 17 % and 28 % of patients in **Studies III** and **II**, respectively. This aligns with previous studies of older patients showing that executive functions are commonly impaired in chronic states post stroke, with one-tenth to one-third of patients impaired, depending on the task (Barker-Collo et al., 2010; Middleton et al., 2014; Nakling et al., 2017).

Executive impairment did not seem to be associated with particular stroke locations, such as frontal versus more posterior areas (**Study II**) or subcortical versus cortical areas (**Study I**). Specific frontal areas have been linked with executive subprocesses (Stuss, 2011), but dividing brain areas simply between frontal and more posterior fail in explaining the complex cognitive processing of executive functions (Stuss & Alexander, 2000), and the results of **Study II** align with this. As multiple subcortical areas participate in executive control processes through fronto-subcortical loops (Heyder et al., 2004), the findings of **Study I** are not surprising either. Unexpectedly, thalamic strokes were associated with intact executive functions (**Study II**). This observation contradicts previous literature (e.g., van der Werf, Witter, Uylings, & Jolles, 2000) and may be a random result. In some previous stroke populations, incident white matter changes in stroke patients have been associated with

impaired executive functions (Jaillard et al., 2010; Planton et al., 2011), but in the current study, these findings were not replicated (**Study II**). Together, the results of **Study I** and **Study II** reiterate that executive dysfunction may be associated with strokes in many different locations, not just in frontal areas.

5.3 MEMORY DYSFUNCTION AFTER STROKE

Both verbal and visual memory domains were commonly affected post first-ever stroke at baseline in the present patient cohort, as about one in five showed impaired performance in these domains (**Study III**), which corresponds to previous results on verbal or visual memory (Nys et al., 2007; Rasquin et al., 2002). In one study, using less stringent criteria for impairment yielded higher impairment rates in both working and episodic memory (Jaillard et al., 2009).

Cognitively impaired patients' performance recovered significantly in both verbal and visual memory domains between the baseline and 6-month follow-up; the drop of impairment ratio was the largest in visual memory (**Study III**). This aligns with a previous study, wherein impaired patients recovered significantly after an early post-stroke evaluation in both verbal and visual memory domains; the recovery of visual perception/construction and visual memory were the most common (Nys, van Zandvoort, de Kort, Jansen, van der Worp et al., 2005). Part of what appears to be visual recovery in **Study III**, however, may also be due to chance, since visual memory was measured with only one test. One study with separate patient groups at different time points found no change in verbal or visual memory performance post stroke (Hurford et al., 2013). In an elderly stroke sample not limited to first-ever strokes, patients' verbal memory performance declined significantly between subacute state and 1.5 years, although part of the change may have been due to slight improvements in control group performance (Sachdev, Brodaty, Valenzuela, Lorenz, & Koschera, 2004).

The recovery of memory functions later in the follow-up, after 6 months post stroke, was not significant in the current study (**Study III**). Other studies have demonstrated that most patients' performance remains stable after 6 months post stroke in individual memory tasks such as list learning and complex figure recall (Elgh & Hu, 2019; Rasquin, Lodder et al., 2004).

At a later follow-up, 2 years post stroke, approximately one-tenth of the patients were impaired in verbal memory, but only 4 % in visual memory (**Study III**). In recent studies, memory impairments have not been highly pronounced at chronic states post stroke. In one study, no stroke patients under 65 years were found to be impaired in the list learning of related word clusters 1 year post stroke (Nakling et al., 2017). The visual recall of a complex figure was the most likely impaired cognitive task, with one-fourth of patients impaired (Nakling et al., 2017), but this task does have a high component of executive dysfunction (Somerville, Tremont, & Stern, 2000), which might

explain the discrepancy. Impairment in memory was not pronounced in other older patient groups in chronic state either, with less than one-tenth of patients impaired (Barker-Collo et al., 2010; Middleton et al., 2014).

Subcortical strokes seemed to affect verbal memory performance more than cortical strokes, particularly at baseline (**Study I**). This trend was also observed at 6 months for delayed recall (**Study I**). Memory impairment has been associated with strokes in both subcortical and cortical structures (Godefroy, Roussel, Leclerc, & Leys, 2009; Lim & Alexander, 2009). Comparisons between subcortical and cortical stroke profiles have been mostly limited to general cognition, however, and memory functions have not been specifically studied (Arauz et al., 2014; J. Hochstenbach et al., 1998; Nys et al., 2007; Planton et al., 2011). In one previous study, no differences existed early post stroke in immediate or delayed memory performance between patients with subcortical or cortical strokes (Wilde, 2010), in contrast with the results of the current study (**Study I**). However, stroke size was not controlled for in Wilde's (2010) study, although larger lesions are shown to be associated with poorer memory (Snaphaan & de Leeuw, 2007). In line with the current findings (**Study I**), another study found that patients with predominantly subcortical strokes did, in fact, perform inferiorly in immediate and delayed verbal memory, compared to patients with predominantly cortical strokes 1 year post stroke (Schouten, Schiemanck, Brand, & Post, 2009).

Subcortical areas have been found to be related to memory impairments in other types of studies. Elderly patients with lacunar strokes (Grau-Olivares, Arboix, Bartrés-Faz, & Junqué, 2007) and with subcortical ischemic vascular disease (Jokinen et al., 2006) are found to be impaired in delayed memory performance, and, furthermore, thalamic strokes are found to be associated with memory impairment of both the amnesic and non-amnesic types (van der Werf et al., 2000). Furthermore, additional white matter changes in stroke patients are associated with impaired memory functions in neuropsychological testing (Jaillard et al., 2010; Planton et al., 2011; Snaphaan & de Leeuw, 2007). In **Study I,** the proportion of patients with white matter changes did not differ between patients with subcortical or cortical strokes, but patients with white matter changes were more likely to drop out between the baseline and 6 months post stroke. This may, in part, explain why the difference between subcortical and cortical stroke patients was no longer significant in the verbal memory domain at 6 months. Yet, cognitive recovery did not differ between baseline and 6 months between subcortical and cortical stroke patients (**Study I**), which aligns with a previous study of later cognitive recovery between subacute and chronic states post stroke (Hochstenbach et al., 2003). In line with subcortical and cortical strokes recovering similarly, subcortical stroke patients still performed inferiorly to cortical stroke patients at 6 months in delayed verbal recall (**Study I**).

5.4 ASSOCIATIONS BETWEEN EXECUTIVE AND MEMORY DYSFUNCTION AFTER STROKE

In the current study, associations between executive impairment and memory dysfunction were scrutinized in a homogenous patient sample while controlling for the effects of general intelligence (**Study II**). Patients who were categorized as executively impaired performed inferiorly to the executively intact patients in list learning and immediate recall of a logical story 6 months post stroke. At 2 years, executively impaired patients still performed inferiorly to executively intact patients in list learning, as well as in the delayed recall of the wordlist and the immediate recall of geometric figures.

It is worth noting that in **Study II**, a list of unrelated word was used when comparing patients with and without executive dysfunction. Previous studies (Brooks et al., 2006; Busch et al., 2005; Hill et al., 2012; Tremont et al., 2000; Tremont et al., 2010) have used lists with word clusters, which potentially support patients' learning strategies. When unrelated words are used, higher executive control may be required in learning. Even with a list of only ten words, executive dysfunction was associated with impaired memory performance, as the words were unrelated (**Study II**). In recalling stories, only remembering the first-heard story differed between the executive dysfunction groups at 6 months (**Study II**). It was hypothesized that during the first story, higher demand for executive control was needed, and by the second story, even patients with executive dysfunction were able to infer better strategies. Regrettably, only one story was used at 2 years post stroke, and therefore, the persistence of this phenomenon cannot be evaluated. Executively impaired patients performed inferiorly to executively intact patients in visual memory performance at only the 2-year examination (**Study II**). It was originally (**Study II**) hypothesized that visual problems may have been alleviated after 6 months, but this did not appear to be the case, based on the results of **Study III**. However, the results of **Study II** align with a previous finding of executive dysfunction impairing visual memory performance at only the 1-year follow-up and not at the baseline (Busch et al., 2005). The authors hypothesized that visual memory performance requires more fluid, as opposed to crystallized, abilities, which place greater demand on executive functioning (Busch et al., 2005), but further clarification is needed on why this would become evident only after controlling for the acuteness and severity of brain insult. Contrary to most previous studies on the subject (Brooks et al., 2006; Busch et al., 2005; Tremont et al., 2000; Tremont et al., 2010), in **Study II**, the effects of possible reasoning problems were controlled with the cognitively thorough neuropsychological assessment of reasoning ability, instead of more coarse neurological methods. Thus, it could be concluded that the associations between executive and memory dysfunction were not due to the simultaneous impairment of general intelligence.

Associations between executive dysfunction and memory problems were shown to remain at 2 years (**Study II**). The executive dysfunction group

classification was made at 6 months to stabilize patient data during the follow-up, as well as to provide clinically relevant information to support clinical decision-making on, for example, patients who may require rehabilitation or executive dysfunction-related guidance in adjusting to their post-stroke cognitive abilities. Patients who were classified as executively impaired at 6 months still demonstrated impaired memory performance in the memory tasks requiring active strategy use at 2 years, when compared with the executively intact patients. However, executive dysfunction seemed to be durably associated with impaired active memory usage, as similar associations between executive dysfunction classified at 2 years and memory performance at 2 years were found. The results of **Study II** stress the need to evaluate executive dysfunction and choose, for example, rehabilitation methods accordingly. A focus on metacognitive strategies and active usage of memory strategies, for example, may be beneficial.

5.5 DYSFUNCTION IN OTHER COGNITIVE DOMAINS AFTER STROKE

Executive functioning and memory performance post stroke have been discussed in previous chapters. In this chapter, performance in other cognitive domains is described.

Psychomotor speed was the most commonly impaired cognitive domain, as one-third of the patients showed slowing at baseline (**Study III**). This number is less than in previous studies, where around half of first-ever (Rasquin et al., 2002) and young (Pinter et al., 2019) stroke patients showed psychomotor slowing early post stroke. Psychomotor speed seemed to require the most time to recover, as it was the only domain within which the impairment rate diminished over 5 percentage points between 6 months and 2 years, although this later recovery was not significant (**Study III**). Patients with subcortical strokes were psychomotorically slower than patients with cortical strokes at baseline but no longer significantly so at 6 months (**Study I**). Nearly one-fourth of patients were still impaired in psychomotor speed at 2 years, and this was the cognitive domain most frequently impaired at that timepoint (**Study III**). This matches previous findings, wherein psychomotor speed has been one of the most commonly impaired domains post stroke (Barker-Collo et al., 2010; Middleton et al., 2014; Nakling et al., 2017).

Impairment in visuospatial functions was also prominent at baseline, with one-fourth of patients impaired, and 14 % still impaired at 2 years (**Study III**). Lesion location did not seem to affect visuospatial functioning, as patients with subcortical and cortical strokes were determined as partially equivalent through ICI at baseline, and no differences due to lesion location were found at 6 months, either (**Study I**). In one previous study, visual perception/construction and visual memory were the most commonly recovering domains after early states of stroke (Nys, van Zandvoort, de Kort,

Jansen, van der Worp et al., 2005), but in **Study III**, this recovery seemed to be driven more by the recovery of visual memory than of visuospatial functions. One group found that after subacute state, patients' visuoconstructive performance deteriorated significantly; however, again, part of this seeming recovery may have been due to the control group's simultaneous improvements in performance (Sachdev, Brodaty, Valenzuela, Lorenz, & Koschera, 2004).

The domain of basic language skills was impaired in the smallest proportion of patients, compared with other domains in this clinically well-recovered working-aged population, with only one-tenth of patients impaired at baseline (**Study III**), again, less than in previous studies (Nys et al., 2007; Rasquin, Lodder et al., 2004). In **Study III**, tasks of basic language skills were not even administered to most patients at 2 years, as they had been previously intact. Patients were not excluded due to aphasia in **Study III**, and thus excluding aphasic patients cannot explain the small numbers of patients impaired in basic language skills. Severely aphasic patients were excluded from **Studies I** and **II**, after which basic naming ability did not differ between patients with or without executive dysfunction at 6 months in **Study II**. Mastering basic language skills should not be considered a marker for recovery among the working aged.

Reasoning was assessed in the study protocol at follow-ups, and 14 % of patients were considered impaired at 2 years (**Study III**). Whether reasoning would show more prominent impairment rate at baseline cannot now be answered. No recoveries in reasoning skills were found between 6 months and 2 years (**Study III**). Patients who were categorized as executively impaired also possessed lower reasoning abilities (**Study II**), in line with previous studies (Busch et al., 2005; Duff et al., 2005). Lesion location groups of subcortical or cortical stroke patients did not differ in reasoning abilities at 6 months (**Study I**).

5.6 METHODOLOGICAL CONSIDERATIONS

As a strength, the present study used detailed neuropsychological assessments from the baseline, shortly post stroke, throughout a 2-year follow-up period. The sample was well-defined and homogenous in etiology. This working-aged, first-ever stroke cohort provided a chance to examine cognitive dysfunction and, specifically, executive dysfunction and memory problems in a sample that was relatively free from other confounding factors, such as age-related brain pathology.

In **Study II**, the tendency existed that patients with the largest and most severe strokes were excluded, and in **Study I**, the stroke being restricted to either subcortical or cortical area was a critical inclusion criterion. This may limit the generalizability of the results to the most affected patients. Furthermore, for example, severely aphasic patients were excluded in **Studies**

I and **II** to allow better analyses, and these aphasic patients were likely among the most affected patients. In **Study III**, however, aphasia was not an exclusion criterion, and it should not directly affect cognitive impairment rates. In **Study III**, the excluded patients were more likely to be executively impaired and possess lower psychomotor speeds at baseline than the included patients. Furthermore, lower education levels appeared to be more likely among the excluded patients than among the included patients (**Studies II** and **III**). However, most demographic and clinical variables were similar between excluded and included patients and between dropped-out and re-evaluated patients in **Studies I–III**, which indicates that the results may be reasonably well generalizable to the working aged. The cognitive impairment rates may have been larger if all drop-outs could have been included.

Cognitively impaired patients were older and less educated than cognitively intact patients (**Study III**). This demonstrates a known problem in categorizing patients based on norms when matching all demographics is not possible. The control group comprised 50 matched persons from similar background as the patients. However, the control group was not sufficiently large to be divided into age- and education-based subgroups for better comparison. In assessing recovery, however, all patient and control groups were compared with their own behaviors, and thus demographic differences should not significantly affect the recovery results (**Study III**).

The brain imaging information in the present study was derived from scans taken for clinical purposes. Not all clinically diagnosed strokes were visible in the available imaging data, and only a portion of the patients were scanned with MRI, while the rest were scanned with CT. In **Studies I–III**, using the clinical images may have hindered the characterization and analysis of particularly coinciding brain changes. Using clinical images may have reduced the number of patients available for **Study I**, wherein a visible stroke was a prerequisite for inclusion, thus also reducing the power of analysis. Possessing only the clinical images may have slightly hindered the possibilities to assess specific lesion locations' associations with executive dysfunction (**Study II**). Moreover, including patients based on clinical stroke diagnosis with good stroke treatment and without visible strokes may also partly explain the relatively low impairment rate of the patient group, compared with some other studies wherein only patients with visible lesions were included.

Slightly different definitions for cognitive impairment were used in **Studies I–III**. This explains some of the differences in results between these studies. Since different criteria to denote impairment yield different proportions of patients being classified as impaired, some studies report, for example, rates of both mild and severe cognitive impairment (e.g., Barker-Collo et al., 2010; Middleton et al., 2014)

In the current study, the baseline neuropsychological evaluations were performed when patients were sufficiently stable for discharge (to the home or active rehabilitation facilities). This aimed to diminish the chances that fluctuating conditions at the most acute state would impair replicability of the

evaluation results and the predictability of future performance. Some cognitive recovery between baseline and 6 months may still be due to these early changing conditions, yet the results appeared fairly consistent. Neuropsychological rehabilitation was received by some patients, and it generally lasted beyond 6 months post stroke. Thus, ending rehabilitation should not explain why little recovery was seen later post stroke. The interval between the patient and control group assessments differed, which may have produced differing learning effects due to repeated testing, to some extent.

Importantly, in the present study, lesion size was controlled for when the effects of subcortical and cortical strokes were compared (**Study I**), which has not been previously done. Highlighting the need to control for lesion size, cognitively impaired patients also had larger infarctions than cognitively intact patients (**Study III**). Furthermore, lesion location classification to subcortical and cortical strokes was mutually exclusive in **Study I**, enabling better evaluation of specific stroke locations' associations to cognitive functioning.

5.7 CONCLUDING NOTES

According to the present results, long-lasting cognitive impairment is frequent even in working-aged stroke patients who have recovered neurologically well. It is important to examine, in particular, working-aged patients with high cognitive demands in life and many expected productive years to come with a thorough neuropsychological battery, to uncover possible cognitive impairments. The gold standard to assess cognitive impairment is – and should remain – neuropsychological evaluation covering multiple cognitive domains (Cumming et al., 2013). Indeed, it has been recommended that in future studies, the assessment of "cognition" should be improved and harmonized (Brainin et al., 2015).

The results of the current studies of high functioning patients align with the growing body of evidence among different-aged stroke patients demonstrating that cognitive profiles post stroke tend to be dominated by psychomotor slowing and executive dysfunction, rather than pronounced memory dysfunction (Barker-Collo et al., 2010; Cumming et al., 2013; Hurford et al., 2013; Middleton et al., 2014; Nakling et al., 2017; Sachdev, Brodaty, Valenzuela, Lorentz, Looi et al., 2004).

In the present studies, the commonly identified executive dysfunction was also found to be long lasting. Executive impairment was associated with memory tasks that were less structured and thus demanded better use of active memory strategies. This may have resulted in secondary problems in memory performance after executive dysfunction. Different causes of memory dysfunction call for different coping strategies, and the role of executive dysfunction should be considered when inspecting memory performance. The present results suggest that subcortical strokes may impair memory performance more than do cortical strokes. Moreover, patients with cortical

strokes were not found to be inferior to patients with subcortical strokes in any of the studied cognitive domains. In clinical practice, it is not safe to assume any specific type of lesion to be benign, and all stroke subgroups should be inspected for cognitive impairment early post stroke; it seems important to follow-up with all stroke patient groups as well.

Among the stroke patients participating in the present studies, the majority of cognitive recovery occurred within the first 6 months post stroke. This highlights the importance of the detailed description of cognitive impairments early post stroke. Thorough early assessment facilitates the careful planning of, for example, neuropsychological rehabilitation, which should begin early post stroke to sufficiently guide the cognitive recovery process. However, rehabilitation should not be restricted to the first 6 months, as cognitive problems were found to persist throughout the 2-year follow-up, and since cognitive problems were related to mood symptoms in follow-ups in the present study. In clinical practice, the persistence of cognitive impairments should be followed up, and longer rehabilitation periods should be allowed to facilitate compensatory coping strategies in patients with altered cognition and mood.

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