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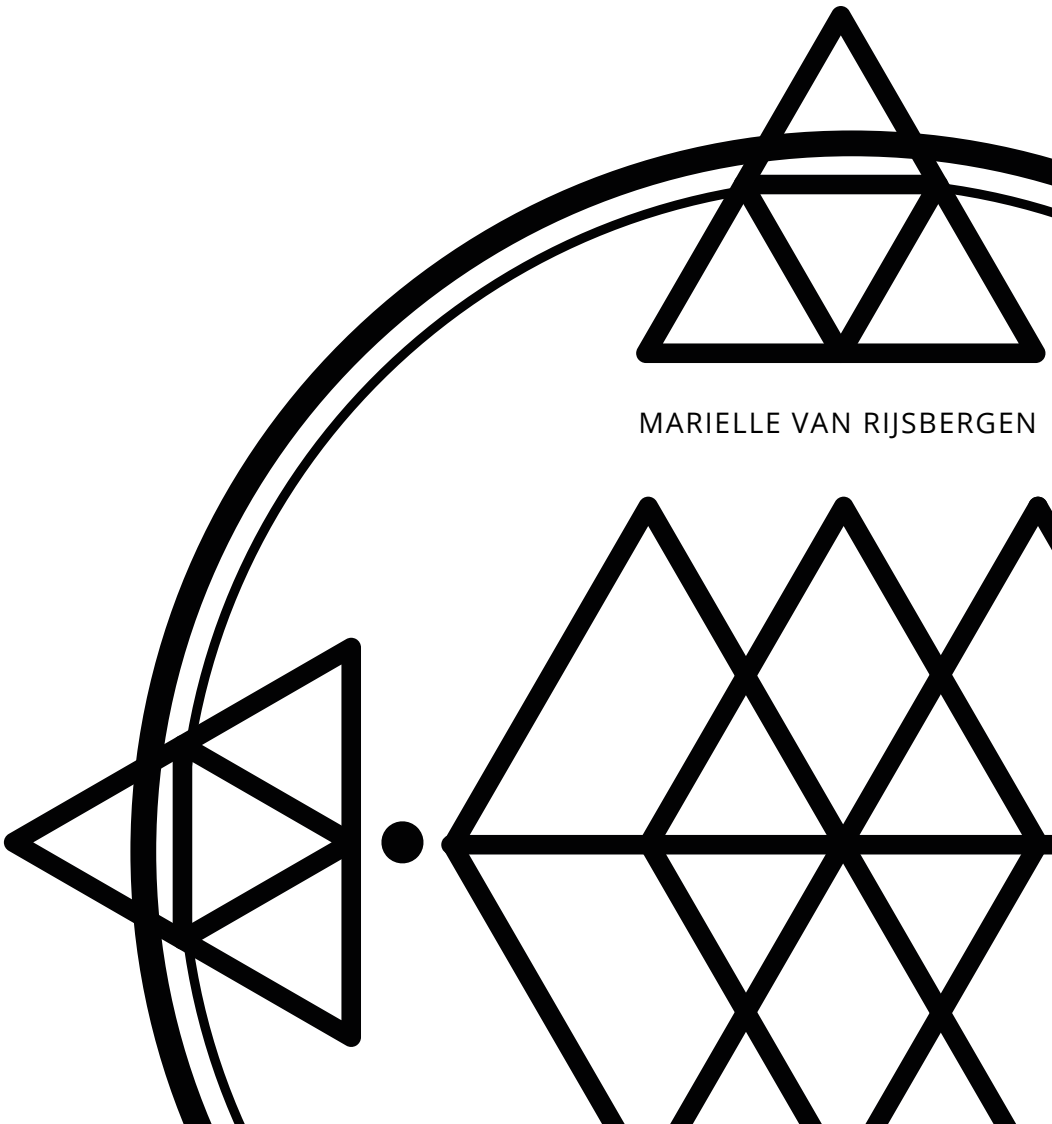

MARIELLE VAN RIJSBERGEN

SUBJECTIVE COGNITIVE COMPLAINTS AFTER STROKE:
PREVALENCE, DETERMINANTS AND COURSE OVER TIME

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan Tilburg University
op gezag van de rector magnificus, prof. dr. E.H.L. Aarts,
in het openbaar te verdedigen ten overstaan van een door het college
voor promoties aangewezen commissie in de aula van de Universiteit
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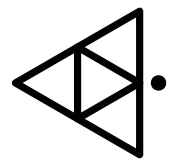
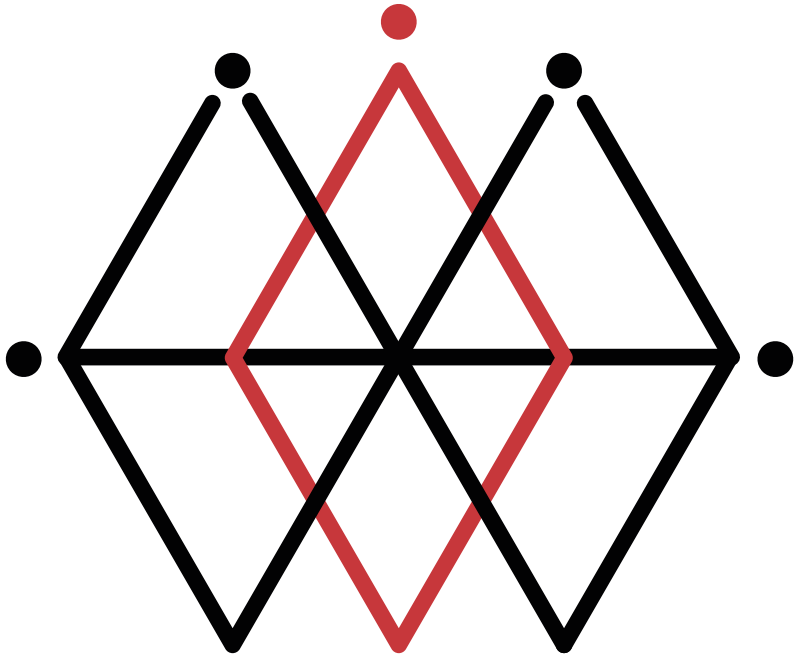


Onze grootste overwinning is niet dat we nooit falen,
maar dat we telkens als we struikelen weer opstaan.

CONFUCIUS



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CHAPTER 1

GENERAL INTRODUCTION

GENERAL INTRODUCTION

Stroke is a common condition, affecting globally almost 17 million and in Europe approximately 1.1 million people each year [1, 2]. It is one of the leading causes of death and disability worldwide [2, 3]. Survivors frequently have to deal with physical and psychological impairments, which negatively affect quality of life (QoL) [4-9]. A stroke occurs when blood flow to a part of the brain is interrupted as a result of either blockage (called an ischemic stroke) or rupture (called a hemorrhagic stroke) of a blood vessel [10, 11]. In general, approximately 80% of the strokes are ischemic, 15% are caused by a bleeding inside the brain (intracerebral hemorrhage) and 5% result from a bleeding in the subarachnoid space surrounding the brain (subarachnoid hemorrhage) [11, 12]. Brain cells in the affected area are deprived of oxygen and glucose and begin to die within minutes following vessel occlusion or rupture [11]. Depending on the location and severity of the brain damage, temporary or permanent loss of functions in the physical, cognitive and/or psychological domain occurs, and this can in turn negatively affect well-being [4-8].

The primary goal of the research presented in this dissertation is to document the prevalence and course of subjective cognitive complaints after stroke and to establish whether there are specific factors (stroke-related, physical, cognitive and/or psychological characteristics) associated with these patient-perceived cognitive problems. These objectives are examined in the multidisciplinary longitudinal **COMP**laints **A**fter **S**troke (COMPAS) study. This general introduction provides the clinical and theoretical background of the investigation and describes: [1] the epidemiology and risk factors of stroke, followed by [2] the common consequences of stroke on the physical, cognitive and psychological domain, [3] subjective cognitive complaints after stroke, [4] the COMPAS study design and procedures, and [5] definition of subjective cognitive complaints in this project. Finally the aims and outline of this dissertation are described.

1. EPIDEMIOLOGY AND RISK FACTORS

In The Netherlands, approximately 41,000 people suffer from a stroke on an annual basis, which roughly translates into an incidence of approximately 113 people each day [13]. Due to improvements in treatment, the mortality associated with acute stroke has decreased [1, 2]. Within the first month, the mortality rate is about 7% after an ischemic stroke and 30% after an intracerebral hemorrhage [1, 14]. Most of the patients survive their stroke [1] and after their hospitalization, approximately 50% of the patients are discharged home, 40% go to a rehabilitation facility, and about 10% are discharged to a nursing home [14]. It is estimated that in The Netherlands, the prevalence of individuals with stroke is more than 175,000, of which many have to deal with mild to moderate physical or mental disabilities [1, 2, 9, 13]. Stroke survivors therefore comprise a large group of patients frequently requiring clinical management [1].

Multiple characteristics, known as 'vascular risk factors', are associated with an increased risk of having a stroke, including: increasing age, male sex, family history of stroke, hypertension, hyperlipidemia, ischemic heart disease, atrial fibrillation, diabetes mellitus, smoking, excessive alcohol consumption, drug abuse, physical inactivity, unhealthy diet, obesity, psychosocial stress, depression, migraine with aura, birth control pills and hormone replacement therapy [14, 15]. Many of these risk factors are modifiable and can be treated or controlled in order to lower the likelihood of having a stroke [15]. The improved post-stroke survival over the past decades has in turn shifted research and clinical attention towards the long-term physical and mental consequences of stroke, including patient-reported outcomes and subjective cognitive complaints.

2. CONSEQUENCES OF STROKE

Physical domain

Stroke survivors frequently experience one or more physical disabilities. Most prominent are motor deficits (e.g., muscle weakness, paralysis, spasticity, contractures), sensory disturbances (e.g., pain, increased or decreased sensitivity), communication problems (e.g., aphasia, dysarthria), visual field deficits (e.g., hemianopia), neglect, seizures and sleeping disorders (e.g., insomnia or obstructive sleep apnea) [11]. These consequences often lead to substantial problems with activities of daily living (ADL) [16]. Approximately 66% of patients surviving a stroke eventually recover sufficiently well enough to be able to live independently at home, while one in three patients require continued assistance with one or more daily life activities [13, 14].

Cognitive domain

Cognitive functioning has been frequently studied among stroke survivors. The majority of these studies focus on objective cognitive performance using global cognitive screening tests (e.g., the Mini Mental State Examination [17]) or neuropsychological tests covering one or more domains (e.g., memory, attention, processing speed, executive functions). Incident stroke is often associated with cognitive decline both early after stroke (acute and subacute phase) and in the months and years thereafter (chronic phase) [18-20]. The prevalence of cognitive impairment ranges from 10% to 82%, depending on the criteria used to define impairment, the time interval of assessment chosen after stroke and the patient sample evaluated [20]. The cognitive profile after stroke typically includes impairments in the domains of processing speed, attention and executive function [18, 20]. Whereas memory initially tends to be relatively intact, problems become more prominent when time after stroke passes (prevalence rate varying between 23% and 55% at 3 months post-stroke) [21]. As described below, marked improvements in cognitive function can occur in the first months after stroke and recovery can be facilitated by rehabilitation programs [18]. Longitudinal studies show that approximately 70% of the patients remain cognitively stable over time, about 10% deteriorate and develop dementia, and 20-30% will partially recover in terms of cognitive function [19, 22, 23]. These estimates reflect general trends and substantial individual differences exist in the nature and pattern of post-stroke recovery and also whether or not the patient will regain their pre-stroke level of cognitive function.

Post-stroke cognitive impairment is associated with a lower QoL in both patients and their caregivers, more institutionalization, higher health-care costs and a higher mortality rate [5, 18, 19]. Even mild cognitive deficits may reduce participation in rehabilitation programs and may cause poor adherence to secondary prevention treatments [18, 24]. Evidence suggests that cognitive impairment tends to be associated with depressive symptoms, but the relationship is complex [25, 26]. Whereas depressive symptoms early after stroke independently increase the risk of cognitive impairment, cognitive impairment also predicts the development of depressive symptoms later on [20, 27]. Cognitive rehabilitation programs, focusing mainly on learning how to cope with the cognitive impairments (e.g., by learning how to apply adequate compensation strategies) are relatively successful [18], but more research is needed to further evaluate the short-term and long-term effects of cognitive and psychosocial rehabilitation in patients surviving stroke.

Psychological domain

Psychological distress and neuropsychiatric disturbances are prevalent after stroke [28]. Depression and anxiety are among the most frequently studied mood disturbances among stroke survivors [28, 29]. About 31% of the patients experience depression between 1 and 5 years after stroke [28, 30]. Predictors of post-stroke depression include: pre-stroke depression, post-stroke anxiety and cognitive impairment, stroke severity and associated physical disability, lack of social support and networks and maladaptive coping skills [26-30]. The recovery rate of post-stroke depression is modest and the risk of recurrent depressive episodes in the years after stroke is high [28]. Post-stroke depression is also associated with increased mortality, negatively affects functional outcome and QoL, and predicts caregiver depression [26, 28, 30].

About 25% of the patients report anxiety after their stroke [28, 31]. Predictors of post-stroke anxiety include previous depression or anxiety and alcohol abuse, young age, female sex, cognitive impairment, aphasia, history of insomnia, ADL dependency, inability to work, being single or having no social contacts outside the family [28, 31]. It is associated with worse social functioning and poor QoL [28]. Although anxiety in patients surviving stroke can be treated, between 25% and 50% of the patients continue to have anxiety symptoms or a clinical anxiety disorder [28].

Fatigue

Fatigue is one of the most common sequelae of stroke, reported by more than 50% of the survivors, even when stroke is relatively mild and there is little disability [32-35]. The onset of fatigue often occurs immediately after stroke [32, 33, 35].

About one-third of the patients recovers over time, but fatigue tends to persist in the majority of patients [33]. Post-stroke fatigue is associated with a lower QoL, more dependency in ADL, institutionalization and poor survival [32-35]. Factors found to be most strongly associated with the prevalence of fatigue after stroke include physical disability and depression [33-36]. Other demographic, social, medical, psychological and biological factors may however also play a role [33, 35, 36]. Whereas pharmacological, physical and/or psychological treatments are used to reduce fatigue, there are currently no specific (successful) evidence-based treatments available [33, 34].

The high prevalence of fatigue, post-stroke depression and anxiety may in part be explained by personality factors and individual differences in coping styles since these traits are associated with increased vulnerability for negative affect [37]. In particular neuroticism and more passive coping styles are linked with psychological distress, such as depression [38], fatigue [39] and a poor health related QoL [38-43].

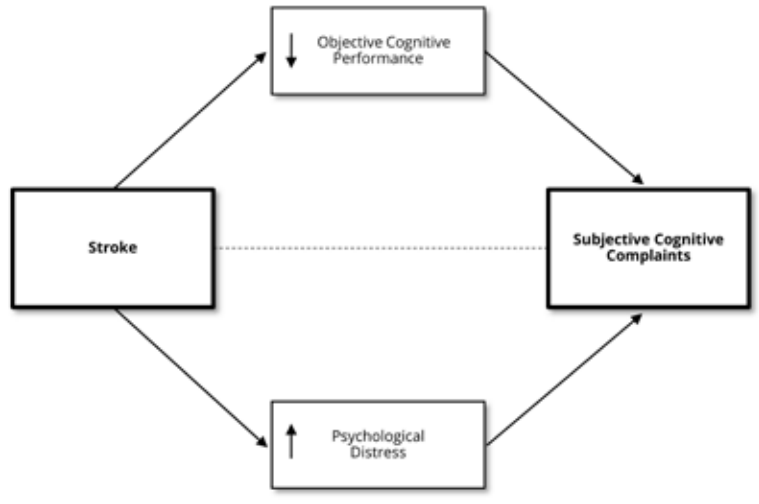
3. SUBJECTIVE COGNITIVE COMPLAINTS

The aforementioned stroke-related physical, cognitive and psychological factors may adversely affect subjectively experienced cognitive abilities after stroke. In contrast to the multiple recent studies on post-stroke objective cognitive performance, less scientific attention has been paid to subjective cognitive complaints (SCC). These refer to the cognitive difficulties stroke survivors themselves report and how much they find them to interfere in their daily lives. From clinical practice and from the small number of studies published on this topic, it is known that SCC are common in all phases (i.e., acute, subacute and chronic phase) after stroke [24, 44-47]. The prevalence estimates of post-stroke SCC vary widely however, depending on the measurement tools, domains of SCC, and when SCC are assessed, with estimates ranging between 28.6% [48] and 92% [49] (see Chapter 2 for an extensive review on SCC after stroke). Complaints regarding the domains mental speed, concentration and memory are most commonly reported [24, 46, 47, 49, 50]. Evidence suggests that there is not a one-to-one relationship between objective cognitive performance based on neuropsychological tests and the patient-reported outcome of SCC [24, 44, 51-55]. Furthermore, individuals' cognitive performances in test situations do not always correspond to performances in daily life activities [49, 54]. Evaluating the objective aspect of cognitive functioning should therefore not be used to draw conclusions about subjective report of cognitive failures (or vice versa). Both factors are however important targets for scientific research and clinical intervention.

SCC, in particular those related to memory, are also common among elderly individuals in the general population without a history of stroke, with up to 50% reporting memory complaints [56, 57]. These memory-related SCC are more prevalent among women, people with lower education, those having psychological distress, somatic disorders, neuroticism and/or vascular risk factors [57-60]. SCC related to memory are considered to be clinically relevant as these complaints are associated with increased healthcare consumption, future cognitive decline and a reduced QoL [56, 57, 60, 61]. The question remains as to whether and how SCC reported after stroke differ from those reported in the elderly population, and whether post-stroke SCC are also linked with outcome measures like QoL.

There is little information on which factors are associated with the experience of SCC after stroke. In addition to a possible link with objective cognitive impairment, studies suggest an association between post-stroke depression and SCC [24, 44, 49], but this relationship is not always found [62]. Also, personality traits and coping styles, at least partly, influence the nature and severity of complaints after stroke in terms of psychological distress and fatigue [37-43]. Personality and coping style may therefore also be interrelated with post-stroke SCC. Which factors increase the likelihood of post-stroke SCC, how these complaints evolve over time, and whether characteristics early after stroke can predict their presence on the long term, are still to be determined. This information might help clinicians detect and perhaps prevent cognition-related concern in patients and in turn ultimately improving post-stroke care. The COMPAS study (outlined in the following paragraph) was set up in an attempt to answer some of these questions. Furthermore, a conceptual model of post-stroke SCC (see Figure 1) provides a general framework for this dissertation.

Figure 1. *Conceptual model of subjective cognitive complaints after stroke*



Note: *Subjective cognitive complaints are common after stroke and may be a direct consequence of the brain damage itself and/or the result of co-occurring poor objective cognitive performance and/or the presence of psychological distress (i.e., depression, anxiety, perceived stress and fatigue) after stroke.*

In summary, SCC is an important patient-reported outcome that is common in post-stroke patients. Multiple factors are associated with SCC, including objective cognitive performance and psychological factors, but the magnitude of these associations is currently not known. This project targets the factors involved in SCC following stroke which may have important implications for patients' QoL and future intervention studies.

4. THE COMPAS STUDY

The studies presented in this dissertation are based on the multicenter, prospective cohort COMPlaints After Stroke (COMPAS) study performed between 2009 and 2014. It is the first longitudinal study exploring post-stroke SCC taking demographic characteristics, clinical variables, objective cognitive performance, psychological distress characteristics and personality traits into account. Details of the COMPAS study are provided in Chapter 3.

Patients with a clinical diagnosis of stroke (either ischemic or hemorrhagic, first-ever or recurrent) and aged ≥ 18 years were consecutively recruited from the stroke units of the Elisabeth-TweeSteden Hospital in Tilburg and the Maxima Medical Center in Veldhoven, The Netherlands. Patients diagnosed with a transient ischemic attack and those with stroke symptoms caused by subarachnoid hemorrhage, tumors or trauma were excluded. Patients having premorbid health problems interfering with cognitive functioning (e.g., cognitive decline, life-threatening progressive diseases such as terminal cancer), a recent history of psychopathology, and/or severe communication difficulties were also excluded from participation. Patients were followed up to 2 years after their stroke during which five assessments were performed, starting at the clinical phase (T0), followed by a neuropsychological and psychological assessments at 3 months (T1), a telephone interview at 6 months (T2), repeated neuropsychological and psychological assessments at 12 months (T3) and 24 months (T4) post-stroke. This dissertation will focus on the T0, T1 and T3 assessments.

Parallel to the target group of patients with stroke, a cohort of community-dwelling healthy participants was recruited for comparison purposes (see Chapter 4). Participants in the comparison group underwent the same assessment protocol as the stroke patients. This 'control group' was recruited among the relatives and social networks of participants and staff involved in the COMPAS study. Spouses of stroke survivors were not included in the comparison group because they have an increased risk of having physical, emotional and/or cognitive complaints themselves due to the fact that their partner has suffered a stroke [63-65]. Data obtained from spouses may be biased as it (partly) depends on what is happening with their proxies, the patients.

In this dissertation, the focus is on post-stroke SCC, the primary outcome measure. This chapter provides additional background information on the definition of SCC.

Details related to the demographic, clinical, cognitive and psychological measures are described in Chapters 3 through 7.

5. DEFINITION OF SUBJECTIVE COGNITIVE COMPLAINTS IN THE COMPAS STUDY

There is no consensus on the definition of SCC in the literature. Whereas some studies have focused on what patients reported as a cognitive problem (e.g., memory complaints, concentration difficulties) irrespective of whether or not it was troublesome in daily life [45, 46, 55], others have made an explicit distinction between self-reported cognitive difficulties that did, versus those that did not interfere with ADL [24, 44, 53]. There are substantial individual differences in the extent to which cognitive problems adversely affect daily life functioning and whether or not they are perceived as having a (negative) impact and/or are a source of concern. In this dissertation, SCC is defined as a psychological construct with two components, namely: *content* (SCC-c), referring to the type/nature of SCC (e.g., memory or executive function complaints) and *worry* (SCC-w), referring to whether or not SCC have an impact on daily life in terms of worry and hindrance. The two components are interrelated: the worry component cannot exist without the content component also being present. In other words, having SCC-w automatically implies that SCC-c are also present. In the COMPAS-study SCC are assessed using the Dutch Cognitive Failures Questionnaire (CFQ; a generic instrument) [66] and the Checklist for Cognitive and Emotional Consequences after stroke (CLCE; a stroke-specific tool) [53] inventory.

6. AIMS AND OUTLINE OF THIS DISSERTATION

The overall aim of this dissertation is to investigate the prevalence, determinants, and course of SCC among adult stroke patients during the first 12 months after hospitalization for stroke. **Chapter 2** describes the results of a systematic review of the literature on post-stroke SCC. In **Chapter 3** the design of the COMPAS study is described, from which data gathered in the clinical phase, at 3 and 12 months are used in the present dissertation. In **Chapter 4** the prevalence and nature of SCC as assessed using both the CFQ and the CLCE, is explored 3 months after stroke. A distinction is made between the nature of the SCC and the impact and related worry of post-stroke SCC. A comparison is made between patients with stroke and non-stroke controls to evaluate which assessment tool, the CLCE or the CFQ, best differentiates between the groups. Based on the results from Chapter 4, we choose to utilize the CLCE instrument as the only measure of SCC in Chapters 5 through 7. **Chapter 5** reports on the cross-sectional association between objective cognitive performance and SCC at 3 months after stroke. Objective cognitive performance is assessed using an extensive neuropsychological battery of tests covering multiple cognitive domains. Standard instruments as well as tests with high ecological validity are included to evaluate which tests are most closely associated with SCC. **Chapter 6** presents the results on the associations between depression, anxiety, perceived stress and fatigue, as well as stable personality

traits and coping style, with SCC at 3 months post-stroke. In **Chapter 7**, the course of SCC from 3 to 12 months after stroke is described and multivariate analyses are used to determine which variables at 3 months predict the presence of SCC at 1-year follow-up. **Chapter 8** provides a general discussion of the main results from the studies presented in this dissertation. Methodological strengths and weaknesses of the studies are considered and this dissertation concludes with suggestions for clinical practice and future research.

REFERENCES

1] Bejot Y, Bailly H, Durier J, Giroud M. Epidemiology of stroke in europe and trends for the 21st century. Presse Med. 2016;45:e391-e398.

2] Bejot Y, Daubail B, Giroud M. Epidemiology of stroke and transient ischemic attacks: Current knowledge and perspectives. Rev Neurol. 2016;172:59-68.

3] Feigin VL, Roth GA, Naghavi M, Parmar P, Krishnamurthi R, Chugh S, et al. Global burden of stroke and risk factors in 188 countries, during 1990-2013: A systematic analysis for the global burden of disease study 2013. Lancet Neurol. 2016;15:913-924.

4] Carod-Artal FJ, Egido JA. Quality of life after stroke: The importance of a good recovery. Cerebrovasc Dis. 2009;27 Suppl 1:204-214.

5] Cumming TB, Brodtmann A, Darby D, Bernhardt J. The importance of cognition to quality of life after stroke. J Psychosom Res. 2014;77:374-379.

6] Ellis C, Grubaugh AL, Egede LE. The association between major depression, health behaviors, and quality of life in adults with stroke. Int J Stroke. 2012;7:536-543.

7] Tang WK, Lau CG, Mok V, Ungvari GS, Wong KS. Impact of anxiety on health-related quality of life after stroke: A cross-sectional study. Arch Phys Med Rehabil. 2013;94:2535-2541.

8] Nys GM, van Zandvoort MJ, van der Worp HB, de Haan EH, de Kort PL, Jansen BP, et al. Early cognitive impairment predicts long-term depressive symptoms and quality of life after stroke. J Neurol Sci. 2006;247:149-156.

9] Boiten J. Cerebrovasculaire aandoeningen. In: Vandermeulen JAM, Derix MMA, Avezaat CJJ, Mulder T, Van Strien JW, eds. Niet-aangeboren hersenletsel bij volwassenen. Maarssen: Reed Business; 2003: 22-37.

10] Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: A statement for healthcare professionals from the american heart association/american stroke association. Stroke. 2013;44:2064-2089.

11] Caplan LR. Caplan's Stroke: A Clinical Approach. 5th Ed. Cambridge; New York: Cambridge University Press; 2016.

12] Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Executive summary: Heart disease and stroke statistics--2013 update: A report from the American Heart Association. Circulation. 2013;127:143-152.

13] Feiten en cijfers beroerte. Hartstichting. https://www.hartstichting.nl/hart-vaten/cijfers/beroerte. Accessed May 21, 2017.

14] Beusmans GHMI, Van Noortwijk-Bonga HGC, Risseeuw NJ, Tjon-A-Tsien MRS, Verstappen WHJM, Burgers JS, et al. NHG-standaard Beroerte. Huisarts Wet. 2013;56:626-638.

15] O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for Ischaemic and Intracerebral Haemorrhagic stroke in 22 countries (the INTERSTROKE study): A case-control study. Lancet. 2010;376:112-123.

16] Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, et al. Guidelines for adult stroke rehabilitation and recovery: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2016;47:e98-e169.

17] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients

for the clinician. J Psychiatr Res. 1975;12:189-198.
18] Cumming TB, Marshall RS, Lazar RM. Stroke, cognitive deficits, and rehabilitation: Still an incomplete picture. Int J Stroke. 2013;8:38-45.
19] Levine DA, Galecki AT, Langa KM, Unverzagt FW, Kabeto MU, Giordani B, et al. Trajectory of cognitive decline after incident stroke. Jama. 2015;314:41-51.
20] de Haan EH, Nys GM, Van Zandvoort MJ. Cognitive function following stroke and vascular cognitive impairment. Curr Opin Neurol. 2006;19:559-564.
21] Snaphaan L, de Leeuw FE. Poststroke memory function in nondemented patients: A systematic review on frequency and neuroimaging correlates. Stroke. 2007;38:198-203.
22] Brainin M, Tuomilehto J, Heiss WD, Bornstein NM, Bath PM, Teuschl Y, et al. Post-stroke cognitive decline: An update and perspectives for clinical research. Eur J Neurol. 2015;22:229-238, e213-226.
23] Liman TG, Heuschmann PU, Endres M, Floel A, Schwab S, Kolominsky-Rabas PL. Changes in cognitive function over 3 years after first-ever stroke and predictors of cognitive impairment and long-term cognitive stability: The Erlangen Stroke Project. Dement Geriatr Cogn Disord. 2011;31:291-299.
24] Duits A, Munnecom T, van Heugten C, van Oostenbrugge RJ. Cognitive complaints in the early phase after stroke are not indicative of cognitive impairment. J Neurol Neurosurg Psychiatry. 2008;79:143-146.
25] Broomfield NM, Laidlaw K, Hickabottom E, Murray MF, Pendrey R, Whittick JE, et al. Post-stroke depression: The case for augmented, individually tailored cognitive behavioural therapy. Clin Psychol Psychother. 2011;18:202-217.
26] Ayerbe L, Ayis S, Wolfe CD, Rudd AG. Natural history, predictors and outcomes of depression after stroke: Systematic review and meta-analysis. Br J Psychiatry. 2013;202:14-21.
27] Robinson RG, Jorge RE. Post-stroke depression: A review. Am J Psychiatry. 2016;173:221-231.
28] Ferro JM, Caeiro L, Figueira ML. Neuropsychiatric sequelae of stroke. Nat Rev Neurol. 2016;12:269-280.
29] Kim JS. Post-stroke mood and emotional disturbances: Pharmacological therapy based on mechanisms. J Stroke. 2016;18:244-255.
30] Hackett M. Depression after stroke and cerebrovascular disease. In: Godefroy O, ed. The Behavioral and Cognitive Neurology of Stroke. Cambridge, UK: Cambridge University Press; 2013:363-374.
31] Menlove L, Crayton E, Kneebone I, Allen-Crooks R, Otto E, Harder H. Predictors of anxiety after stroke: A systematic review of observational studies. J Stroke Cerebrovasc Dis. 2015;24:1107-1117.
32] Cumming TB, Packer M, Kramer SF, English C. The prevalence of fatigue after stroke: A systematic review and meta-analysis. Int J Stroke. 2016;11:968-977.
33] Kutlubaev MA, Mead GE. Fatigue after stroke. In: Godefroy O, ed. The Behavioural and Cognitive Neurology of Stroke. Cambridge, UK: Cambridge University Press; 2013:375-386.
34] Acciarresi M, Bogousslavsky J, Paciaroni M. Post-stroke fatigue: Epidemiology, clinical characteristics and treatment. Eur Neurol. 2014;72:255-261.
35] Wu S, Mead G, Macleod M, Chalder T. Model of understanding fatigue after stroke. Stroke. 2015;46:893-898.
36] Wu S, Barugh A, Macleod M, Mead G. Psychological associations of poststroke fatigue: A systematic review and meta-analysis. Stroke. 2014;45:1778-1783.
37] Galligan NG, Hevey D, Coen RF, Harbison JA. Clarifying the associations between anxiety, depression and fatigue following stroke. J Health Psychol. 2016;21:2863-2871.
38] Aben I, Denollet J, Lousberg R, Verhey F, Wojciechowski F, Honig A. Personality and vulnerability to depression in stroke patients: A 1-year prospective follow-up study. Stroke. 2002;33:2391-2395.
39] Lau CG, Tang WK, Liu XX, Liang HJ, Liang Y, Mok V, et al. Neuroticism and fatigue 3 months after ischemic stroke: A cross-sectional study. Arch Phys Med Rehabil. 2017;98:716-721.
40] van Mierlo M, van Heugten C, Post MW, Hoekstra T, Visser-Meily A. Trajectories of health-related quality of life after stroke: Results from a one-year prospective cohort study. Disabil Rehabil. 2017:1-10.
41] Wei C, Gao J, Chen L, Zhang F, Ma X, Zhang N, et al. Factors associated with post-stroke depression and emotional incontinence: Lesion location and coping styles. Int J Neurosci. 2016;126:623-629.
42] Visser MM, Aben L, Heijenbrok-Kal MH, Busschbach JJV, Ribbers GM. The relative effect of coping strategy and depression on health-related quality of life in patients in the chronic phase after stroke. J Rehabil Med. 2014;46:514-519.
43] Lo Buono V, Corallo F, Bramanti P, Marino S. Coping strategies and health-related quality of life after stroke. J Health Psychol. 2017;22:16-28.
44] Nijsse B, van Heugten CM, van Mierlo ML, Post MW, de Kort PL, Visser-Meily JM. Psychological factors are associated with subjective cognitive complaints 2 months post-stroke. Neuropsychol Rehabil. 2017:99-115.
45] Visser-Keizer AC, Meyboom-de Jong B, Deelman BG, Berg IJ, Gerritsen MJ. Subjective changes in emotion, cognition and behaviour after stroke: Factors affecting the perception of patients and partners. J Clin Exp Neuropsychol. 2002;24:1032-1045.
46] Hochstenbach J, Prigatano G, Mulder T. Patients' and relatives' reports of disturbances 9 months after stroke: Subjective changes in physical functioning, cognition, emotion, and behavior. Arch Phys Med Rehabil. 2005;86:1587-1593.
47] Wendel K, Risberg J, Pessah-Rasmussen H, Stahl A, Iwarsson S. Long-term cognitive functional limitations post stroke: Objective assessment compared with self-evaluations and spouse reports. Int J Rehabil Res. 2008;31:231-239.
48] Pendlebury ST, Mariz J, Bull L, Mehta Z, Rothwell PM. MOCA, ACE-R, and MMSE versus the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery after TIA and Stroke. Stroke. 2012;43:464-469.
49] Lamb F, Anderson J, Saling M, Dewey H. Predictors of subjective cognitive complaint in post-acute older adult stroke patients. Arch Phys Med Rehabil. 2013;94:1747-1752.
50] Tinson DJ, Lincoln NB. Subjective memory impairment after stroke. Int Disabil Stud. 1987;9:6-9.
51] Lincoln NB, Tinson DJ. The relation between subjective and objective memory impairment after stroke. Br J Clin Psychol. 1989;28:61-65.
52] Davis AM, Cockburn JM, Wade DT. A subjective memory assessment questionnaire for use with elderly people after stroke. Clin Rehabil. 1995;9:238-244.
53] van Heugten C, Rasquin S, Winkens I, Beusmans G, Verhey F. Checklist for cognitive and emotional consequences following stroke (CLCE-24): Development, usability and quality of the self-report version. Clin Neurol Neurosurg.

2007;109:257-262.
54] Winkens I, Van Heugten CM, Fasotti L, Wade DT. Reliability and validity of two new instruments for measuring aspects of mental slowness in the daily lives of stroke patients. Neuropsychol Rehabil. 2009;19:64-85.
55] Aben L, Ponds RW, Heijenbrok-Kal MH, Visser MM, Busschbach JJ, Ribbers GM. Memory complaints in chronic stroke patients are predicted by memory self-efficacy rather than memory capacity. Cerebrovasc Dis. 2011;31:566-572.
56] Jonker C, Geerlings MI, Schmand B. Are memory complaints predictive for dementia? A review of clinical and population-based studies. Int J Geriatr Psychiatry. 2000;15:983-991.
57] Reid LM, Maclullich AM. Subjective memory complaints and cognitive impairment in older people. Dement Geriatr Cogn Disord. 2006;22:471-485.
58] Paradise MB, Glozier NS, Naismith SL, Davenport TA, Hickie IB. Subjective memory complaints, vascular risk factors and psychological distress in the middle-aged: A cross-sectional study. BMC Psychiatry. 2011;11:108.
59] Jorm AF, Butterworth P, Anstey KJ, Christensen H, Easteal S, Maller J, et al. Memory complaints in a community sample aged 60-64 years: Associations with cognitive functioning, psychiatric symptoms, medical conditions, apoe genotype, hippocampus and amygdala volumes, and white-matter hyperintensities. Psychol Med. 2004;34:1495-1506.
60] Comijs HC, Deeg DJ, Dik MG, Twisk JW, Jonker C. Memory complaints; the association with psycho-affective and health problems and the role of personality characteristics. A 6-year follow-up study. J Affect Disord. 2002;72:157-165.
61] Mol M, Carpay M, Ramakers I, Rozendaal N, Verhey F, Jolles J. The effect of perceived forgetfulness on quality of life in older adults; a qualitative review. Int J Geriatr Psychiatry. 2007;22:393-400.
62] Narasimhalu K, Wiryasaputra L, Sitoh YY, Kandiah N. Post-stroke subjective cognitive impairment is associated with acute lacunar infarcts in the basal ganglia. Eur J Neurol. 2013;20:547-551.
63] Berg A, Palomaki H, Lonnqvist J, Lehtihalmes M, Kaste M. Depression among caregivers of stroke survivors. Stroke. 2005;36:639-643.
64] Rigby H, Gubitz G, Phillips S. A systematic review of caregiver burden following stroke. Int J Stroke. 2009;4:285-292.
65] van Exel NJ, Koopmanschap MA, van den Berg B, Brouwer WB, van den Bos GA. Burden of informal caregiving for stroke patients. Identification of caregivers at risk of adverse health effects. Cerebrovasc Dis. 2005;19:11-17.
66] Broadbent DE, Cooper PF, FitzGerald P, Parkes KR. The cognitive failures questionnaire (cfq) and its correlates. Br J Clin Psychol. 1982;21 (Pt 1):1-16.

CHAPTER 2

SUBJECTIVE COGNITIVE COMPLAINTS AFTER STROKE:
A SYSTEMATIC REVIEW

BASED ON:

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ABSTRACT

Objective: Most studies to date have assessed post-stroke cognitive impairment objectively, whereas less attention is paid to subjective cognitive complaints (SCC). We therefore systematically searched the literature to summarize and evaluate the current knowledge about post-stroke SCC.

Methods: Articles were included in this review if the study evaluated SCC in adult stroke survivors and the publication was an original empirical article from which the full-text was available. There were no year or language restrictions.

Results: Twenty-six studies were found on post-stroke SCC. There is a huge heterogeneity among these studies with respect to stroke sample, SCC definitions and instruments used, but they all showed that SCC are very common after stroke. Other main findings are that SCC tend to increase over time and that there is moderate agreement between patients and their proxies on prevalence and severity of patients' SCC. Furthermore, SCC are inconsistently associated with current depressive symptoms and objective cognitive performance, whereas they may predict future emotional and cognitive functioning.

Conclusions: This review highlights that post-stroke SCC are highly prevalent and are potentially relevant to post-stroke care. More research is however needed to gain further insight into post-stroke SCC, to be able to accurately inform patients and relatives, and to develop adequate treatment programs. Based on the limitations of the studies to date, suggestions are made for future research to further improve patient-centered care in stroke survivors reporting SCC.

INTRODUCTION

Cognitive impairment is common in both the acute and chronic phase after stroke, and can be evaluated either objectively (using neuropsychological tests), or subjectively (using self-report measures or interviews). To date, most studies investigating post-stroke cognition have focused on objective assessment whereas subjective cognitive complaints (SCC), defined as whether individuals report cognitive difficulties and if so what these are and whether they are irritating and/or worrying for them, are too often ignored.

Research on SCC in the general population has typically focused on memory complaints, whereas recent studies have begun to suggest that complaints about other cognitive domains (including attention, executive functioning, language etc.) should also be assessed [1]. The consensus in this field is that SCC are important to attend to because they negatively affect daily functioning and quality of life (QoL), increase health care consumption, and may be an early indication of cognitive decline [1-4]. In this systematic review, we aim to summarize and evaluate what is currently known from the literature about SCC in stroke patients.

METHODS

Search strategy

A systematic literature search was conducted in MEDLINE, EMBASE, PsychINFO, Cochrane library databases, and ClinicalTrials.gov using key words and synonyms (see the Appendix of this chapter, Computerized search strategy). The search was last updated in April 2013. Relevant articles published after this date are briefly discussed in the General Discussion (Chapter 8) in this dissertation. Reference lists of all included articles were additionally hand-searched for relevant publications. Research articles were included if they met the following criteria: (1) the study evaluated patient-reported SCC in adult (≥ 18 years) stroke survivors, and (2) the publication was an original empirical article from which the full-text was available. Searches were not limited by language or year of publication. When studies reported identical results using the same patient sample, only the most recent publication was included.

Quality assessment

Two reviewers (MR and RM) independently assessed titles, abstracts and full-text reports on eligibility. The quality of each of the selected articles was subsequently determined by these raters using a 14-item checklist (Table 1). We devised our own tool for this review because an internationally accepted instrument for assessing the quality of observational epidemiological studies does not currently exist [5]. Disagreement between the raters about eligibility and/or quality was solved by discussion. The scores each article received were intended for descriptive purposes only.

***Table 1**. List of criteria for assessing the quality of studies included*

Each criterion receiving 1 point if:
Study Sample
A. Specific inclusion and exclusion criteria are reported.
B. Participants are compared with non-participants with regard to baseline factors (e.g., sociodemographic and stroke characteristics).
C. Time interval after stroke (i.e., mean and standard deviation or median and range) is reported.
D. More than one sociodemographic variable (e.g., age, sex, education level) of the patient group is described.
E. More than one clinical variable (e.g., type of stroke, lesion side, location, stroke severity) is reported.
F. When SCC are evaluated in a longitudinal study, number or percentages of drop-outs are reported.
Design
G. The study is prospectively designed.
H. The process of data collection is described sufficiently to make replication possible.
I. SCC are one of the primary or secondary outcomes.
J. SCC are evaluated by a psychometrically sound measure (i.e., published questionnaire or standardized interview rather than questions devised by the authors).
K. At least one of the following variables is considered in relation to SCC: demographic characteristics, clinical characteristics, objective cognitive functioning, emotional complaints (e.g., depression or anxiety), fatigue, stress, personality characteristics, or coping style.
L. Post-stroke SCC are compared with those found in a non-stroke control sample.
M. Agreement between self- and proxy-assessment of SCC is evaluated.
Statistical Methods
N. Recognized statistical techniques are used to analyze the SCC data.

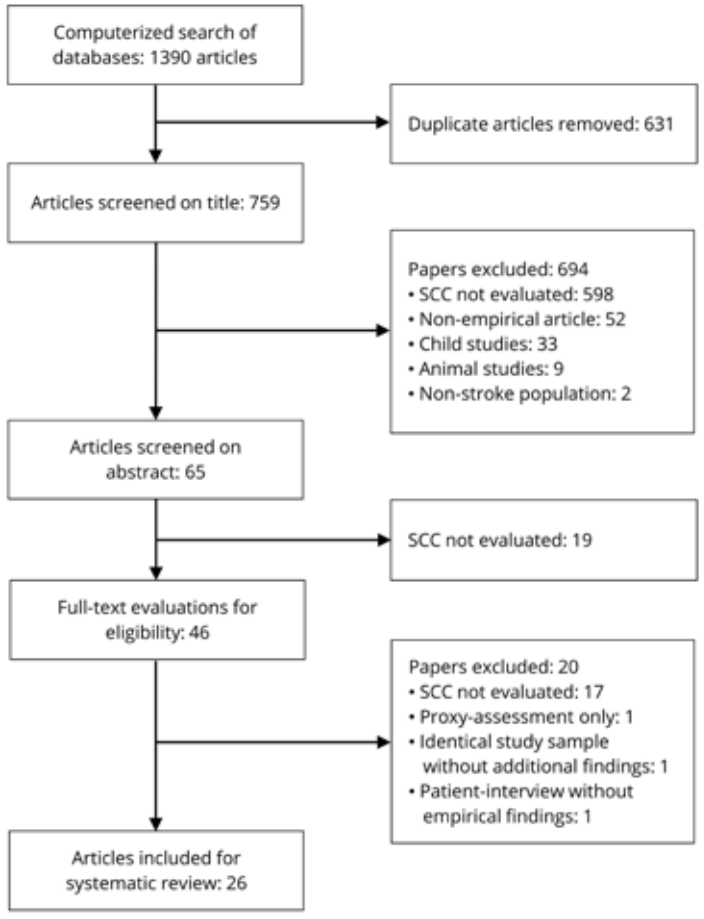
***Abbreviation**: SCC, subjective cognitieve complaints.*

RESULTS

Study characteristics

A total of 26 studies were included (see Figure 1). These were published between 1987 and 2013. Table 2 gives an overview of the study characteristics. Twenty studies used a cross-sectional design [6-25], 4 were longitudinal [26-29], and 2 were randomized controlled trials [30, 31]. Five out of the 26 compared stroke patients to a non-stroke control group [8, 13, 15, 24, 27]. There is a huge sample size range across the publications (ranging from 12 [31] to 1251 [16] participants) and the samples are quite heterogenic. Twelve studies for example included only first-ever stroke patients [6-9, 12, 16, 20, 21, 28-31], 8 evaluated individuals with a specific stroke type or location (i.e., hemorrhagic stroke [16], lacunar stroke [18, 25], stroke associated with small vessel disease [17], thalamic stroke [13], unilateral stroke [21], left-sided location [26], right-sided location [11]), and 9 focused on independent and home-living subjects only [6, 9, 10, 15, 20, 22, 26, 28, 30]. Mean age of the patients in 3 studies was ≤ 50 years (i.e., young stroke) [9, 11, 20], while the other publications were more focused on the elderly population (mean age up to 73 years [19]) [6-10, 12-18, 21, 23-31]. Studies furthermore differed in the time interval after stroke when the patients were assessed: 9 publications evaluated them in the early phase (≤ 6 months after stroke) [8, 9, 11, 15, 17, 18, 21, 24, 25], 13 in the chronic phase (> 6 months post-stroke) [6, 7, 10, 12-14, 16, 19, 20, 22-24, 30] and 4 in both phases [26-29].

***Figure 1.** Flow-chart of the selection procedure*



***Abbreviation:** SCC, subjective cognitive complaints.*

Quality of the articles included

Criteria that were fulfilled by the majority of the studies included: the description of inclusion and exclusion criteria (25 studies) [6-10, 12-31] and the demographic characteristics of the study sample (26 studies) [6-31], the prospective nature of the design (24 studies) [6-8, 10-25, 27-31], adequate report of the data collection procedure (26 studies) [6-31], and the use of recognized statistical techniques (24 studies) [6, 8-16, 18-31]. Furthermore, in 24 publications [6-10, 12-28, 30, 31] SCC was included as one of the main outcomes and 22 studies [6, 8, 9, 12-16, 18-22, 24-31] evaluated associations of SCC with at least one other variable (e.g., demographic characteristics, emotional functioning, or objective cognitive performance, OCP); see Table A1 in the Appendix for a detailed overview of the points received by each study.

Important limitations of studies included: the use of unvalidated methods for assessing SCC (i.e., a self-developed questionnaire or semi-structured interview; 12 studies) [7, 10, 16-23, 25, 32]; a limited description of differences between participants and non-participants (21 studies) [8-15, 17-19, 21, 23-31]; absence of a non-stroke control group (20 studies) [6, 7, 9, 10, 12, 14, 16-23, 25, 26, 28-31]; or lack of proxy-assessment (20 studies) [6-9, 11-13, 16-20, 23-26, 28-31], see Table A1 in the Appendix. These publications were however also included because this is the first review on post-stroke SCC and we wanted to summarize what is currently known from the literature on this topic. Moreover, in clinical practice, SCC are frequently evaluated using self-developed interview questions and it has to be determined yet whether this method is by definition worse than the validated instruments currently available for measuring SCC.

Definition and assessment

There is no consensus among the studies on how to define SCC (see Table 2). First of all, studies differed in the content of SCC, in other words what did patients themselves name as a cognitive problem or difficulty in their daily lives. Although 14 studies assessed global SCC or SCC on multiple domains [7, 9, 10, 12, 13, 15-17, 20-22, 25, 28, 29], 12 focused on one particular aspect, including: memory (8 studies) [6, 8, 14, 18, 19, 27, 30, 31], mental speed (2 studies) [23, 24], attention (1 study) [11], or language (1 study) [26].

Table 2. *Characteristics of studies included, grouped by design*

First Author, Year, Country	Design	Stroke population	Time of measurement since stroke	SCC definition	SCC assessment
Duits, 2008, The Netherlands [9]	Cross-sectional, retrospective	61 first-ever ischemic stroke patients discharged home from stroke unit	Mean: 5 weeks	Cognitive complaints hindering daily life	CLCE-24
Lincoln, 1989, United Kingdom [14] *	Cross-sectional	78 patients admitted to hospital	7 months	Subjective memory impairment	EMQ
Visser-Keizer, 2002, The Netherlands [21]	Cross-sectional	113 first-ever unilateral ischemic patients admitted to hospital	Mean: 115 days	Subjective cognitive change	Study-specific questionnaire: 20 cognitive items
Carlsson, 2003, Sweden [7]	Cross-sectional	75 first-ever ischemic or hemorrhagic patients admitted to stroke unit, living with a spouse	12 months	Experienced mental fatigability, memory dysfunction, concentration difficulties	Semi-structured interview: no details given
Mok, 2004, China [17] †	Cross-sectional	75 patients with a stroke associated with small vessel disease, admitted to stroke unit	3 months	Cognitive complaints	Semi-structured interview: no details given
Hochstenbach, 2005, The Netherlands [10]	Cross-sectional	172 patients with first-ever or recurrent ischemic or hemorrhagic stroke, or subarachnoid hemorrhage, currently living at home	Mean: 9.8 months	Subjective cognitive changes	Semi-structured interview: 16 cognitive items
Winkens, 2006, The Netherlands [23]	Cross-sectional	13 patients from rehabilitation center, suffering from mental slowness	Mean: 23.5 months	Perceived cognitive problems related to mental slowness	Semi-structured interview about everyday problems related to memory, attention, executive functioning, mental speed
Wendel, 2008, Sweden [22]	Cross-sectional	84 first-ever or recurrent ischemic or hemorrhagic stroke patients from a stroke register, having cognitive functional limitations in the acute phase, being mobile, independent, and living in ordinary housing at follow-up	Median: 26 months	Subjective cognitive functional limitations	Study-specific questionnaire: 18 cognitive items

Table 2. *Continued*

First Author, Year, Country	Design	Stroke population	Time of measurement since stroke	SCC definition	SCC assessment
Röding, 2009, Sweden [20]	Cross-sectional	867 patients with first-ever ischemic or hemorrhagic stroke, from a stroke register, currently independent in daily life personal activities	Range: 8-30 months	Self-perceived deteriorated cognitive function	Study-specific questionnaire: no details given
Aben, 2011, The Netherlands [6]	Cross-sectional	136 first-ever ischemic or hemorrhagic stroke patients discharged from rehabilitation center, currently living independently	Mean: 51.3 months	Memory complaints	1 question: "do you experience problems in your memory functioning due to your stroke?"
McKevitt, 2011, United Kingdom [16]	Cross-sectional	1251 patients with first-ever subarachnoidal, intracerebral, or cerebral hemorrhage, or unspecified stroke from a national register and 2 study population registers	Range: 1-5 years	Self-reported cognitive changes	Study-specific questionnaire: 4 cognitive items
Xiong, 2011, China [25] †	Cross-sectional	75 lacunar stroke patients admitted to a stroke unit	3 months	Cognitive complaints	3 questions: Do you have worse memory / worse problem solving ability / slower thinking after stroke?
Narasimhalu, 2013, Singapore [18]	Cross-sectional	97 lacunar stroke patients from a tertiary institute	Mean: 3 months	Subjective cognitive impairment	1 question: "Have you been experiencing problems with your memory / other mental functions?"
Pendlebury, 2012, United Kingdom [19]	Cross-sectional	91 first-ever or recurrent stroke or TIA patients	≥ 1 year	Subjective memory complaint	1 question: "Do you think you have more problems with your memory than most?"
Lamb, 2013, Australia [12]	Cross-sectional	25 first-ever ischemic stroke patients from specialized stroke units, having a relatively good neurological recovery	Mean: 6.6 months	Subjective cognitive complaint	ABNAS
Davis, 1995, United Kingdom [8]	Cross-sectional, case-control	50 first-ever ischemic or hemorrhagic stroke (in)patients from rehabilitation center, day centers and day hospitals	Median: 4 months	Subjective memory ability	SMAQ

Table 2. *Continued*

First Author, Year, Country	Design	Stroke population	Time of measurement since stroke	SCC definition	SCC assessment
Keller, 1995, Germany [11]	Cross-sectional, case-control	17 right-sided ischemic or hemorrhagic stroke patients from neuropsychology department	Mean: 3.2 months	Subjectively perceived attention deficits	Study-specific questionnaire: 12 cognitive items
Liebermann, 2013, Germany [13]	Cross-sectional, case-control	68 ischemic thalamic stroke patients from neurology department	Mean: 37.2 months	Subjective cognitive impairment	MAC-S, FEDA, DEX
Martin, 2002, France [15]	Cross-sectional, case-control, matched	214 home-living patients from rehabilitation centers	Mean: 2.7 months	Subjective cognitive difficulties	EBIQ
Winkens, 2009, The Netherlands [24]	Cross-sectional, case-control, matched	37 first-ever or recurrent ischemic or hemorrhagic stroke patients from rehabilitation centers	Mean: 234 days	Perceived consequences of mental slowness	MSQ
Doyle, 2006, United States [26]	Longitudinal, Retrospective	37 single left-hemisphere thrombo-embolic or hemorrhagic community-dwelling stroke patients with objective aphasia	3 months 12 months	Subjective communication difficulty and distress	BOSS Difficulty and Distress scale
van Heugten, 2007, The Netherlands [28]	Longitudinal	69 first-ever cerebral ischemic or hemorrhagic stroke patients admitted to hospital, living at home 6 months post-stroke	6 months 12 months	Cognitive complaints	CLCE-24
Wilz, 2007, Germany [29]	Longitudinal	57 first-ever stroke patients admitted to rehabilitation center and assessed twice	3 months 15 months	Perceived cognitive functioning	PCRS
Tinson, 1987, United Kingdom [27] *	Longitudinal, case-control	Baseline: 94 patients admitted to hospital Follow-up: 75 of the patients assessed at baseline	1 month 7 months	Subjective memory impairment	EMQ
Doornhein, 1998, The Netherlands [31]	Randomized Controlled Trial	12 first-ever cerebral stroke patients currently staying in rehabilitation center, and having subjective and objective memory problems	Range: 3-5 months	Subjective memory problems	MQ

Table 2. *Continued*

First Author, Year, Country	Design	Stroke population	Time of measurement since stroke	SCC definition	SCC assessment
Aben, 2013, The Netherlands [30]	Randomized Controlled Trial	153 first-ever ischemic or hemorrhagic stroke patients from rehabilitation center, living independently, and having subjective memory complaints	Mean: 53.9 months	Memory complaints	Semi-structured interview: several items considering memory complaints

*The studies marked by * or † used the same population, but reported different results. Studies were designed prospectively unless specified otherwise. Cases were not matched to controls unless specified otherwise.* ***Abbreviations****: ABNAS, A-B Neuropsychological Assessment Schedule; BOSS, Burden of Stroke Scale; CLCE-24, Checklist for Cognitive and Emotional consequences following stroke; DEX, Dysexecutive Questionnaire; EBIQ, European Brain Injury Questionnaire; EMQ, Everyday Memory Questionnaire; FEDA, 'Fragebogen Erlebter Defizite der Aufmerksamkeit'; MAC-S, Memory Assessment Clinics Self-Rating Scale; MIA, Metamemory in Adulthood Questionnaire; MSQ, Mental Slowness Questionnaire; MQ, Memory Questionnaire; NR, not reported; PCRS, Patient Competency Rating Scale; SCC, subjective cognitive complaints; SMAQ, Subjective Memory Assessment Questionnaire; TIA, transient ischemic attack.*

Differences between the studies were also observed in whether researchers evaluated if the reported difficulties (i.e., the content of SCC) were experienced as irritating, worrying and/or something to complain about (i.e., worry component of SCC). Eight studies used the term 'complaints' in their definition of SCC, which implies that these researchers attempted to evaluate not only the content but also the degree of hinder and/or worry patients reported [6, 9, 12, 17, 19, 25, 28, 30]. However, from these 8 studies, only Aben et al. [6] and Duits et al. [9] made an explicit distinction between cognitive difficulties experienced as annoying/hindering in daily life (i.e., SCC-worry) versus patient-reported impairments which were not that troublesome (i.e., no SCC-worry).

In accordance with this variation in definition, the methods used to assess SCC also differ across the publications (see Table 2). Fourteen studies used a validated instrument (e.g., the Everyday Memory Questionnaire [14, 27], or the Checklist for Cognitive and Emotional consequences following stroke; CLCE [9, 28]) [6, 8, 12, 13, 15, 24, 26, 29-31], while 12 studies used only one or more self-developed and unvalidated questions to assess SCC (e.g., 'do you experience problems in your memory functioning due to your stroke?' [6], or 'have you been experiencing problems with your memory or other mental functions?' [18]) [7, 10, 11, 16, 17, 19-23, 25].

Prevalence, pattern and course of subjective cognitive complaints

The prevalence of SCC, assessed between 1 month [9] and 54 months [30] post-stroke, varied between 28.6% [19] and 92.0% [12], with SCC about memory, mental speed, and concentration found to be the most common (see Table 3). Although language-related SCC (i.e., patient-reported difficulty in reading, writing, and speaking) seemed to be less prevalent, these were still named by more than 30% of the patients [10, 12, 16, 22].

Five studies evaluated the effect of time since stroke on SCC prevalence using either a cross-sectional [6, 8, 15], or a longitudinal design [27, 29]. Three of them (1 cross-sectional [15], and 2 longitudinal studies [27, 29]) found heightened SCC with increased time after stroke (cross-sectional: tested within the first year versus after 1 year post-stroke [15]; longitudinal: 1 versus 7 months [27]; 3 versus 15 months after stroke [29]).

Table 3. *Prevalence and pattern of subjective cognitive complaints in stroke patients*

First author	% with SCC	Pattern SCC
Lamb [12]	92	Cognitive slowing: 76%
		Memory difficulties: 72%
		Poor concentration: 68%
		Language: 64%
Winkens [24]	84	NR
Wendel [22]	80	Poor concentration: 45%
		Decreased ability to talk and express oneself: 44%
		Difficulty in remembering planned activities: 44%
		Difficulty in remembering things heard, read, seen: 44%
		Difficulty in doing things simultaneously: 42%
		Difficulty in writing: 38%
Visser-Keizer [21]	80	Impaired memory left-sided stroke: 49%
		Impaired memory right-sided stroke: 38%
Aben [30]	75	NR
Duits [9]	74	Mental slowness: 46%
		Attention problems: 38%
		Recent memory problems: 38%
Aben [6]	74	NR
Van Heugten [28]	73	Doing 2 things at once: 30%
Mok [17]	52	Memory problems: 92%
		Slow thinking: 74%
Xiong [25]	43	Memory symptoms: 94%
		Decreased mental speed: 75%
Narasimhalu [18]	31	NR
Pendlebury [19]	29	NR
Carlsson [7]	NR	Memory dysfunction: 55%
		Concentration difficulties: 42%
Hochstenbach [10]	NR	Forgetfulness: 61%
		Difficulty in writing: 56%
		Mental slowness: 56%
		Poor concentration: 55%
		Inability to do 2 things simultaneously: 53%
		Difficulty in reading: 48%
		Difficulty speaking: 32%
Winkens [23]	NR	Difficulty doing 2 things at the same time: 100%
		Slower information processing: > 80%
		Difficulty storing information in memory: > 80%
		No longer perform tasks automatically: > 80%
		Reacting slowly or slow decision making: 46% – 77%
		Difficulty retrieving information from memory: 46% – 77%
		Being easily distracted: 46% – 77%
Röding [20]	NR	Concentration problems: 60%
		Difficulty completing a task: 60%
		Problems staying in crowded environments: 58%
		Memory problems: 57%
		Decreased simultaneous capability: 52%
		Problems with engaging in discussions: 52%
McKevitt [16]	NR	Concentration problems: 45%
		Memory problems: 43%
		Difficulty speaking: 34%
Tinson [27]	NR	Reported by > 10% (no further details given):
		Losing things around the house
		Forgetting when something happened
		Forgetting things that were told recently
		Rambling on about unimportant things
		Finding that a word is on the 'tip of the tongue'
		Forgetting important details about the day before
		Forgetting where things are normally kept

Abbreviations: *NR, not reported; SCC, subjective cognitive complaints.*

Demographic and clinical characteristics associated with prevalence of subjective cognitive complaints

The effect from sex and age on prevalence of SCC is inconsistent (see Table 4). Although 1 publication found higher age to be associated with more SCC [6], 6 did not observe this relationship [8, 13, 15, 18, 25, 28]. Similarly, 2 studies demonstrated SCC to be more common among women than among men [15, 20], but 6 did not [6, 12, 13, 18, 25, 28]. Other demographic variables found not to be associated with post-stroke SCC include: education level [6, 15, 18, 25, 28], marital status [6, 21] and residence at time of the assessment [27] (see Table 4).

Studies have also failed to find a link between prevalence of SCC and the following clinical variables: stroke type (i.e., ischemic or hemorrhagic) [6, 33], severity [25], lesion size [13], lesion side [6, 13, 15, 21], hemiplegia [15, 27], comorbidity [18], vascular risk factors [18, 25], or neurodegenerative characteristics (e.g., white matter hyperintensities, temporal lobe atrophy) [25] (see Table 4). However, 2 studies did find an association between the experience of SCC and a specific stroke location [13, 18]. Liebermann et al. [13] showed that memory-related SCC were more prevalent among patients with a lesion involving the anterior thalamus than among patients with more posterior lesions. This effect of lesion location was not seen when SCC about attention or executive functioning were considered. Narasimhalu et al. [18] furthermore demonstrated that patients with a basal ganglia stroke reported more SCC than those with a brain stem, thalamic, cerebellar, or frontal stroke.

Subjective cognitive complaints in stroke patients versus controls

Post-stroke SCC were compared with those found in non-stroke groups (matched to the stroke sample on major demographic characteristics like age, sex, education level) in 5 out of the 26 studies [8, 13, 15, 24, 27]. The control group included: orthopedic patients [27], patients with a history of transient ischemic attack (TIA) [13], or a sample from the general population [8, 15, 24]. Four out of these 5 studies reported that SCC were more common and more troublesome after stroke than in the control

group [8, 11, 15, 27]. Only Liebermann et al. [13] did not find such a difference when they compared ischemic thalamic stroke patients to people with a history of a TIA.

Self-assessment versus proxy-assessment of subjective cognitive complaints

Six studies reported results from both self- and proxy-assessment [10, 14, 15, 21, 22, 27]. Five found moderate to high agreement between patients and proxies on the prevalence of post-stroke SCC, especially when the content of SCC was concrete and observable (e.g., self-reported disorientation or difficulty in writing or speaking) [10, 14, 15, 22, 27]. Visser-Keizer et al. [21] showed agreement to be dependent on lesion side: although reports of partners and left-hemisphere patients were similar, partners of right-sided patients reported both more frequent and severe changes than the patients themselves did. Tinson and Lincoln [27] furthermore demonstrated that partners and patients disagreed on the course of SCC; while partners reported an improvement, patients said SCC increased over time.

Table 4. *Effect of demographic and clinical characteristics on prevalence of post-stroke subjective cognitive complaints*

Variable	Effect found
Age	Old > young [6]
	No effect [8, 13, 15, 18, 25, 28]
Sex	Women > men [15, 20]
	No effect [6, 12, 13, 18, 25, 28]
Education (low, middle, or high)	No effect [6, 15, 18, 25, 28]
Partner (yes or no)	No effect [6, 21]
Employment (employed or not employed)	No effect [15]
Residence (at home or in hospital)	No effect [27]
Type of stroke (ischemic or hemorrhagic)	No effect [6]
Stroke location	Anterior thalamus [13], Basal ganglia [26],
	No effect [25]
Stroke severity (NIHSS-score)	No effect [25]
Lesion side (left, right, bilateral)	No effect [6, 12, 13, 15, 21, 25]
Lesion size or volume	No effect [13, 25]
White matter lesions (volume, presence)	No effect [18, 25]
Cerebral atrophy	No effect [25]
Medial temporal lobe atrophy	No effect [18]
Presence of silent infarcts	No effect [25]
Hemiplegia (presence and/or side)	No effect [15, 27]
Comorbidity and vascular risk factors	No effect [18, 25]

None of these studies reported correlation coefficients. ***Abbreviation:*** *NIHSS, National Institutes of Health Stroke Scale.*

Link between objective cognitive performance and subjective cognitive complaints

Fourteen studies evaluated whether OCP (assessed using neuropsychological tests) were associated with SCC by comparing patients with SCC to those without SCC on OCP and/or computing correlations between the two (see Table 5) [6, 8, 9, 11, 12, 14, 15, 18, 19, 22, 24-26, 28]. The results were inconsistent: while 8 studies found that patients with SCC also had poorer OCP on at least one cognitive test than those without SCC [8, 11, 14, 18, 22, 25, 26, 28], 6 studies did not observe such a relationship [6, 9, 12, 15, 19, 24]. Patients with SCC did not have impaired OCP or vice versa [12, 19], did not differ in OCP from those without SCC [6, 9, 15] or the correlation between SCC and OCP was not significant [24].

The association between OCP and SCC after stroke was most frequently evaluated on the cognitive domains memory, language, and executive functioning, with the highest correlation (r = 0.71) found on the memory domain by Davis et al. [8] (see Table 5).

Lincoln and Tinson [14] furthermore evaluated whether the association between memory-related OCP and SCC was affected by the OCP tests' degree of ecological validity. They found that SCC were more strongly correlated to OCP when this was assessed with a test resembling everyday tasks (i.e., the Rivermead Behavioral Memory Test), compared with conventional memory tests (i.e., Digit Span, Paired Associate Learning). Aben et al. [6] and Duits et al. [9] however, reported contradictory findings (see Table 5). Furthermore, SCC was not found to be associated with OCP in 3 of the 4 studies measuring executive functioning, irrespective of whether conventional or ecologically valid tests were used (see Table 5) [6, 9, 18, 25].

Table 5. *Subjective cognitive complaints versus objective cognitive performance in stroke patients*

Cognitive domain assessed	Test used	OCP in patients with vs. without SCC	Correlation between SCC and OCP
Premorbid intelligence [8]	NART	SCC < No-SCC	0.48
General cognitive function [12, 18, 25, 28]	ADAS-cog	SCC < No-SCC [25]	NR [25]
	RBNAS	NR [12]	-0.18 (n.s.) [12]
	MMSE	SCC < No-SCC [18, 25, 28]	NR [18, 28, 25]
	CAMCOG	SCC < No-SCC [28]	NR [28]
	MoCA	SCC = No-SCC [18]	NR [18]
Memory [6, 8, 9, 14, 24]	RBMT	SCC = No-SCC [6, 9]	-0.46 [14] to 0.71 [8] or n.s. [9]
	AVLT	SCC = No-SCC [6, 24]	NR [6, 24]
	Logical memory	NR [14]	-0.23 [14]
	Digit span	NR [14]	-0.26 [14]
	Paired associate learning	NR [14]	-0.21 [14]
	Recurring figures test	NR [14]	-0.09 (n.s.) [14]
Attention [11, 24]	TMT	NR [24]	n.s. [24]
	Stroop Color-Word task	NR [24]	n.s. [24]
	PAT	NR [11]	0.61 [11]
Mental speed [24]	MSOT	NR	n.s.
	PASAT	NR	n.s.
	SDMT	NR	n.s.
	Simple reaction time task	NR	n.s.
Language [6, 15, 26]	Token Test	SCC = No-SCC [6]	NR [6]
	55-RTT	NR [26]	-0.31 (n.s.) [26]
	BNT	SCC = No-SCC [6]	NR [6]
	Clinical evaluation	SCC = No-SCC [15]	NR [15]
	SPICA	NR [26]	-0.42 to -0.38 [26]
	BDAE severity rating scale	NR [26]	-0.52 to -0.50 [26]
Executive functions [6, 9, 18, 25]	BADS Zoo map test	SCC = No-SCC [6]	NR [6]
	BADS key search test	SCC = No-SCC [6]	NR [6]
	Word fluency	SCC = No-SCC [6, 9]	n.s. [9] or NR [6]
	TMT	SCC = No-SCC [6, 9]	n.s. [9] or NR [6]
	MADRS I/P	SCC < No-SCC [25]	NR [25]
	FAB	SCC = No-SCC [18]	NR [18]
	Tower of London	SCC = No-SCC [9]	n.s. [9]
	Raven's colored progressive matrices	SCC = No-SCC [9]	n.s. [9]

The correlations reported in the table are significant unless specified otherwise. Results on SCC – OCP from the studies by Pendlebury et al. [19] and Wendel et al. [22] were not described in the current table, since results on the group differences and/or correlations were not given in their publication. ***Signs:*** *< patients with SCC have significantly lower OCP than those without SCC; = patients with SCC do not differ significantly on OCP from those without SCC.* ***Abbreviations:*** *ADAS-Cog, Alzheimer's Disease Assessment Scale – cognitive subset; AVLT, Auditory Verbal Learning Test; BADS, Behavioral Assessment of the Dysexecutive Syndrome; BDAE, Boston Diagnostic Aphasia Examination; BNT, Boston Naming Test; CAMCOG, part of the Cambridge Examination for Mental Disorders in the Elderly; FAB, Frontal Assesment Battery; MDRS I/P, Mattis Dementia Rating Scale Initiation/Perseveration subset; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment; MSOT, Mental Slowness Observation Test; NART, National Adult Reading Test; No-SCC, patients without subjective cognitive complaints; NR, results about association not reported; n.s., no significant association; OCP, objective cognitive performance; PASAT, Paced Auditory Serial Addition Task; PAT, Pigache Attention Task; RBMT, Rivermead Behavioral Memory Test; RBNAS, Repeatable Battery for the Assessment of Neuropsychological Status; RTT, Revised Token Test; SDMT, Symbol Digit Modalities Test; SCC, subjective cognitive complaints; SPICA, Shortened Porch Index of Communicative Abilities; TMT, Trail Making Test.*

Depression and other psychosocial factors associated with subjective cognitive complaints

Depressive symptoms were found to be positively related to post-stroke SCC in 7 of the 8 publications evaluating this association [6, 9, 12, 15, 24-26]. Only Narasimhalu et al. [18] did not observe this link in lacunar stroke patients. They explained this contradictory result as being due to the low prevalence of self-reported depression in their patients.

Other psychosocial factors found to be linked with SCC include: high neuroticism [6], memory self-efficacy [6], low social support [16], having difficulties in social interactions [16], transport abilities [16], work and leisure activities [16], low income and increased expenses [16]. On the other hand, extraversion and coping style were shown not to be associated with SCC [6], and findings with respect to independency in basic activities of daily living (ADL) and fatigue were mixed; both higher [24] and lower ADL [8] were found to be associated with SCC, whereas fatigue was linked with SCC in one [24] but not in another study [12].

Treatment of subjective cognitive complaints

Studies on treatment of post-stroke SCC are scarce; only 2 randomized controlled trials were found and both used a different training program [30, 31]. Doornhein et al. [31] showed that in patients with demonstrable memory deficits, the trained memory skills were improved after a 4-week period of strategy training, but there was no transfer to other tasks and it had no effect on SCC. More recently, Aben et al. [30] focused on a training to improve memory self-efficacy in patients with memory related post-stroke SCC. It was suggested that SCC would improve as a result of higher self-efficacy. The training was successful for self-efficacy, but the effect on SCC was, however, not reported.

Predictive value of subjective cognitive complaints

Two studies evaluated whether SCC could predict future OCP and emotional functioning [28, 29]. Van Heugten et al. [28] demonstrated that SCC measured at 6 months post-stroke predicted poor OCP assessed 1 year after stroke, and Wilz and Barskova [29] showed that SCC evaluated at 3 months post-stroke predicted depressive symptoms at 15 months.

DISCUSSION

To the best of our knowledge, this is the first systematic review on post-stroke SCC. A main finding is that there is large heterogeneity among the studies with respect to stroke sample, SCC definitions and the instruments used. Based on the studies included in this review, the following conclusions can be drawn: SCC are common after stroke, they tend to increase over time, and there is moderate agreement between patients and their proxies on prevalence and severity of patients' SCC. Furthermore, SCC are inconsistently associated with demographic and clinical characteristics, OCP and depressive symptoms, and may predict future cognitive and emotional functioning.

One of the main problems is that there is no 'gold standard' on how to define SCC. Based on this review, we suggest to defined SCC as a construct comprising two components, including: *content*, referring to the cognitive difficulties or problems patients report themselves, and *worry*, referring to the subjective impact of SCC in terms of interference in ADL, annoyance and/or a source of concern. An individual may report 'cognitive impairments' or 'limited cognitive functioning', but this does not mean that they are also hindered by or complain about them. This distinction is potentially relevant, not least because presence of SCC is one of the original Petersen criteria for the diagnosis of Mild Cognitive Impairment (although these criteria are also a matter of debate) [34]. Consensus on the definition of SCC is, therefore, important.

Agreement between patients and proxies on prevalence and severity of SCC was highest for concrete and observable self-reported difficulties. Low agreement may be because of the patients' reduced capacity to recognize problems (i.e., anosognosia), denial, or emotional distress of patients and/or their partners [10, 21]. These findings indicate that relying on proxy reports exclusively when evaluating SCC in stroke survivors, has its own limitations.

The studies included show that SCC tend to be related both to current impaired OCP and to depressive symptoms. The evidence is however mixed: 8 studies found SCC to be associated with OCP [8, 11, 14, 18, 22, 25, 28] (6 did not) [6, 9, 12, 15, 19, 24] and 7 studies found a link between SCC and depressive symptoms [6, 9, 12, 15, 24-26] (1 did not) [18]. Researchers concluded that patients with impaired OCP do not necessarily have SCC and vice versa, while those without SCC are not by definition the ones with good OCP [12, 19, 22, 24]. SCC seem to be more related to co-morbid depressive symptoms instead. However, the inconsistent results on the relationship between SCC, OCP and depression may just be an effect of the methods used to assess these variables (e.g., validated or unvalidated methods, and ecologically valid or more conventional tests) and/or the stroke sample studied (e.g., patients living independently at home or those from a rehabilitation center). Furthermore, according to the reported correlations between OCP and SCC (see Table 5), OCP was more strongly linked to SCC in the memory (rather than other) domains. This finding could be explained as being because of: [1] the fact that memory-related SCC are the most frequently evaluated in the literature, [2] correlations with other cognitive domains were not always reported (e.g., none were given for executive functioning) and/or [3] a real effect: stroke patients are simply more aware of their memory functioning than they are of the other cognitive domains. In summary, the presence and nature of the relationships between SCC, OCP and depression are still a matter of debate.

Post-stroke SCC may predict future cognitive decline, a link which has also been found in the non-stroke elderly population in which memory-related SCC have been the most frequently studied SCC [3]. Available evidence suggests that subjective memory complaints among healthy elderly are predictive for future cognitive decline and/or dementia and are associated with neurodegenerative changes in the brain (e.g., reduced volumes of the hippocampus and amygdala, and/or white matter lesions) [35-37]. Subjective memory complaints in this population are, therefore, usually taken seriously as they might 'just' be an age-related problem, but also a symptom of depression or a possible early sign of dementia [1, 3]. Whether this also applies to other domains of SCC (not only those related to memory, but also those regarding attention, mental speed, language, or executive functions) and to post-stroke SCC, has yet to be determined. Because stroke in itself is already a risk factor for subsequent dementia [38], these patients in particular could benefit from early detection of cognitive deterioration. It might therefore be useful to closely monitor patients with SCC after their stroke for signals of cognitive decline.

Future research may address the limitations of the studies described in this review. Conclusions about causality, differences with other populations and generalizability of the results to the stroke population as a whole are limited because a proportion of the studies used a cross-sectional design, did not include a control group and/or focused on specific subsamples of stroke patients (e.g., home-living patients only). Other topics which can be evaluated in research include: the exploration of a detailed risk-profile for developing SCC after stroke, the underlying mechanisms involved, and their impact on ADL, QoL and health care consumption. Some recommendations for future studies on post-stroke SCC are provided in Table 6. These suggestions may be helpful in preparing the design and methodology of future studies examining post-stroke SCC. A limitation of the current review is that the quality of the individual articles was not evaluated. Although the overall quality of the majority of studies was good, future systematic reviews and meta-analyses may shed additional light on the prevalence of SCC in patients after stroke.

Table 6. *Recommendations for future research on post-stroke SCC*

- Define SCC making a clear distinction between the two components *content* and *worry*.
- Use a validated instrument in addition to self-developed questions to assess SCC (e.g., the CFQ [40] or the CLCE [28]) in order to make replication possible and determine course over time.
- Use both patient and proxy-reports to assess patients' SCC, do not rely exclusively on proxies.
- Provide a detailed description of the demographic (e.g., age, sex, education level, IQ) and clinical characteristics (e.g., stroke subtype, first-ever or recurrent stroke, patients living at home or having clinical rehabilitation) of the stroke sample studied.
- Include a control group comparable to the stroke patients on demographics characteristics (see above).
- Measure OCP on multiple domains and include an estimation of premorbid cognitive functioning (using for example the IQCODE [41])
- Evaluate a wide range of relevant factors in relation to post-stroke SCC, including for example demographic variables, clinical characteristics (e.g., information obtained by CT or MRI scans), personality traits, coping style, emotional state, life events, stress, fatigue, level of awareness, and ADL.
- Use a prospective, longitudinal design with multiple assessments of SCC.
- Report both the prevalence of SCC and the correlations between SCC and other variables evaluated (see above).

Abbreviations: *ADL, activities of daily living; CT, computed tomography; IQ, intelligence quotient; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; MRI, magnetic resonance imaging; OCP, objective cognitive performance; SCC, subjective cognitive complaints.*

It would be helpful that researchers provide a clear definition of what they mean by SCC. We suggest that a distinction is made between *content* (i.e., what cognitive problems or difficulties are reported) and *worry* (i.e., how much impact the SCC have in daily life in terms of interference, annoyance, source of concern). Furthermore, both patients and controls are preferably included using a longitudinal design, and more SCC domains (not just memory) need to be evaluated, while at the same time a wide range of other relevant variables in relation to post-stroke SCC is measured. The COMPlaints After Stroke (COMPAS) study (Chapter 3 [39]) attempts to address post-stroke SCC taking many of these issues into account.

CONCLUSIONS

This review highlights that SCC are very common after stroke and, because of their suggested links with cognitive functioning and psychological well-being, are potentially relevant to post-stroke care. On the other hand, it has also to be noted that while some patients do not report SCC, OCP may still be present and can detrimentally affect treatment success. More research is however needed in order to gain further insight into post-stroke SCC, to be able to more accurately inform patients and relatives and to find key elements for SCC treatment programs. Focusing on what matters to individuals who have recently suffered a stroke, may further improve patient-centered care.

REFERENCES

1] Mark RE, Sitskoorn MM. Are subjective cognitive complaints relevant in preclinical alzheimer's dementia? A review and guidelines for healthcare professionals. Rev Clin Gerontol. 2013;23 61-74.

2] Jorm AF, Butterworth P, Anstey KJ, Christensen H, Easteal S, Maller J, et al. Memory complaints in a community sample aged 60-64 years: Associations with cognitive functioning, psychiatric symptoms, medical conditions, apoe genotype, hippocampus and amygdala volumes, and white-matter hyperintensities. Psychol Med. 2004;34:1495-1506.

3] Reid LM, Maclullich AM. Subjective memory complaints and cognitive impairment in older people. Dement Geriatr Cogn Disord. 2006;22:471-485.

4] Waldorff FB, Siersma V, Waldemar G. Association between subjective memory complaints and health care utilisation: A three-year follow up. BMC Geriatr. 2009;9:43.

5] Sanderson S, Tatt ID, Higgins JP. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: A systematic review and annotated bibliography. Int J Epidemiol. 2007;36:666-676.

6] Aben L, Ponds RW, Heijenbrok-Kal MH, Visser MM, Busschbach JJ, Ribbers GM. Memory complaints in chronic stroke patients are predicted by memory self-efficacy rather than memory capacity. Cerebrovasc Dis. 2011;31:566-572.

7] Carlsson GE, Moller A, Blomstrand C. Consequences of mild stroke in persons <75 years -- a 1-year follow-up. Cerebrovasc Dis. 2003;16:383-388.

8] Davis AM, Cockburn JM, Wade DT, Smith PT. A subjective memory assessment questionnaire for use with elderly people after stroke. Clin Rehabil. 1995;9:238-244.

9] Duits A, Munnecom T, van Heugten C, van Oostenbrugge RJ. Cognitive complaints in the early phase after stroke are not indicative of cognitive impairment. J Neurol Neurosurg Psychiatry. 2008;79:143-146.

10] Hochstenbach J, Prigatano G, Mulder T. Patients' and relatives' reports of disturbances 9 months after stroke: Subjective changes in physical functioning, cognition, emotion, and behavior. Arch Phys Med Rehabil. 2005;86:1587-1593.

11] Keller I, Schlenker A, Pigache RM. Selective impairment of auditory attention following closed head injuries or right cerebrovascular accidents. Cogn Brain Res. 1995;3:9-15.

12] Lamb F, Anderson J, Saling M, Dewey H. Predictors of subjective cognitive complaint in post-acute older adult stroke patients. Arch Phys Med Rehabil. 2013;94:1747-1752.

13] Liebermann D, Ostendorf F, Kopp UA, Kraft A, Bohner G, Nabavi DG, et al. Subjective cognitive-affective status following thalamic stroke. J Neurol. 2013;260:386-396.

14] Lincoln NB, Tinson DJ. The relation between subjective and objective memory impairment after stroke. Br J Clin Psychol. 1989;28 (Pt 1):61-65.

15] Martin C, Dellatolas G, Viguier D, Willadino-Braga L, Deloche G. Subjective experience after stroke. Appl Neuropsychol. 2002;9:148-158.

16] McKevitt C, Fudge N, Redfern J, Sheldenkar A, Crichton S, Rudd AR, et al. Self-reported long-term needs after stroke. Stroke. 2011;42:1398-1403.

17] Mok VC, Wong A, Lam WW, Fan YH, Tang WK, Kwok T, et al. Cognitive

impairment and functional outcome after stroke associated with small vessel disease. J Neurol Neurosurg Psychiatry. 2004;75:560-566.

18] Narasimhalu K, Wiryasaputra L, Sitoh YY, Kandiah N. Post-stroke subjective cognitive impairment is associated with acute lacunar infarcts in the basal ganglia. Eur J Neurol. 2013;20:547-551.

19] Pendlebury ST, Mariz J, Bull L, Mehta Z, Rothwell PM. MOCA, ACE-R, and MMSE versus the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery after TIA and Stroke. Stroke. 2012;43:464-469.

20] Röding J, Glader EL, Malm J, Eriksson M, Lindstrom B. Perceived impaired physical and cognitive functions after stroke in men and women between 18 and 55 years of age--a national survey. Disabil Rehabil. 2009;31:1092-1099.

21] Visser-Keizer AC, Meyboom-de Jong B, Deelman BG, Berg IJ, Gerritsen MJ. Subjective changes in emotion, cognition and behaviour after stroke: Factors affecting the perception of patients and partners. J Clin Exp Neuropsychol. 2002;24:1032-1045.

22] Wendel K, Risberg J, Pessah-Rasmussen H, Stahl A, Iwarsson S. Long-term cognitive functional limitations post stroke: Objective assessment compared with self-evaluations and spouse reports. Int J Rehabil Res. 2008;31:231-239.

23] Winkens I, Van Heugten CM, Fasotti L, Duits AA, Wade DT. Manifestations of mental slowness in the daily life of patients with stroke: A qualitative study. Clin Rehabil. 2006;20:827-834.

24] Winkens I, Van Heugten CM, Fasotti L, Wade DT. Reliability and validity of two new instruments for measuring aspects of mental slowness in the daily lives of stroke patients. Neuropsychol Rehabil. 2009;19:64-85.

25] Xiong YY, Wong A, Mok VC, Tang WK, Lam WW, Kwok TC, et al. Frequency and predictors of proxy-confirmed post-stroke cognitive complaints in lacunar stroke patients without major depression. Int J Geriatr Psychiatry. 2011;26:1144–1151.

26] Doyle PJ, Matthews C, Mikolic JM, Hula W, McNeil MR. Do measures of language impairment predict patient-reported communication difficulty and distress as measured by the Burden Of Stroke Scale (BOSS)? Aphasiology. 2006;20:349-361.

27] Tinson DJ, Lincoln NB. Subjective memory impairment after stroke. Int Disabil Stud. 1987;9:6-9.

28] Van Heugten C, Rasquin S, Winkens I, Beusmans G, Verhey F. Checklist for cognitive and emotional consequences following stroke (CLCE-24): Development, usability and quality of the self-report version. Clin Neurol Neurosurg. 2007;109:257-262.

29] Wilz G, Barskova T. Predictors of psychological and somatic components of poststroke depression: A longitudinal study. Top Stroke Rehabil. 2007;14:25-40.

30] Aben L, Heijenbrok-Kal MH, van Loon EM, Groet E, Ponds RW, Busschbach JJ, et al. Training memory self-efficacy in the chronic stage after stroke: A randomized controlled trial. Neurorehabil Neural Repair. 2013;27:110-117.

31] Doornhein K, De Haan EHF. Cognitive training for memory deficits in stroke patients. Neuropsychol Rehabil. 1998;8:393-400.

32] Jonker C, Geerlings MI, Schmand B. Are memory complaints predictive for dementia? A review of clinical and population-based studies. Int J Geriatr Psychiatry. 2000;15:983-991.

33] Aben L, Kessel MA, Duivenvoorden HJ, Busschbach JJ, Eling PA, Bogert MA, et al. Metamemory and memory test performance in stroke patients. Neuropsychol Rehabil. 2009;19:742-753.

34] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Kokmen E, Tangelos EG. Aging, memory, and mild cognitive impairment. Int Psychogeriatr. 1997;9 Suppl 1:65-69.

35] Stewart R, Dufouil C, Godin O, Ritchie K, Maillard P, Delcroix N, et al. Neuroimaging correlates of subjective memory deficits in a community population. Neurology. 2008;70:1601-1607.

36] Stewart R, Godin O, Crivello F, Maillard P, Mazoyer B, Tzourio C, et al. Longitudinal neuroimaging correlates of subjective memory impairment: 4-year prospective community study. Br J Psychiatry. 2011;198:199-205.

37] Striepens N, Scheef L, Wind A, Popp J, Spottke A, Cooper-Mahkorn D, et al. Volume loss of the medial temporal lobe structures in subjective memory impairment. Dement Geriatr Cogn Disord. 2010;29:75-81.

38] Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: A systematic review and meta-analysis. Lancet Neurol. 2009;8:1006-1018.

39] van Rijsbergen MWA, Mark RE, de Kort PL, Sitskoorn MM. The COMPlaints After Stroke (COMPAS) study: Protocol for a Dutch cohort study on poststroke subjective cognitive complaints. BMJ Open. 2013;3:e003599.

40] Broadbent DE, Cooper PF, FitzGerald P, Parkes KR. The Cognitive Failures Questionnaire (CFQ) and its correlates. Br J Clin Psychol. 1982;21 (Pt 1):1-16.

41] Sunderland A, Wilkins L, Dineen R. Tool use and action planning in apraxia. Neuropsychologia. 2011;49:1275-1286.

CHAPTER 2
APPENDIX

COMPUTERIZED SEARCH STRATEGY

1. stroke*.ti.
2. cva.ti.
3. cerebrovascular accident*.ti.
4. poststroke.ti.
5. post-stroke.ti.
6. apoplexy.ti.
7. 1 or 2 or 3 or 4 or 5 or 6
8. intracerebral.ti.
9. intracranial.ti.
10. cerebral.ti.
11. cerebellar.ti.
12. brain*.ti.
13. vertebrobasilar.ti.
14. 8 or 9 or 10 or 11 or 12 or 13
15. infarct*.ti.
16. ischemi*.ti.
17. ischaemi*.ti.
18. 15 or 16 or 17
19. 14 and 18
20. haemorrhag*.ti.
21. hemorrhag*.ti.
22. haematoma.ti.
23. bleed*.ti.
24. 20 or 21 or 22 or 23
25. 14 and 24
26. 7 or 19 or 25
27. subjective.ti,ab.
28. complain*.ti,ab.
29. self-report*.ti,ab.
30. self-perceiv*.ti,ab.
31. perceiv*.ti,ab.
32. self-assess*.ti,ab.
33. self-evaluat*.ti,ab.
34. experienc*.ti,ab.
35. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. complain*.ti,ab.
37. impairment*.ti,ab.
38. deficit*.ti,ab.
39. problem*.ti,ab.
40. difficult*.ti,ab.
41. loss*.ti,ab.
42. change*.ti,ab.
43. question*.ti,ab.
44. 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45. memory*.ti,ab.
46. forget*.ti,ab.
47. attention*.ti,ab.
48. language.ti,ab.
49. slowness.ti,ab.
50. executive.ti,ab.
51. cogniti*.ti,ab.
52. neuropsychol*.ti,ab.
53. neurobehaviour*.ti,ab.
54. neurobehavior*.ti,ab.
55. neurocognit*.ti,ab.
56. 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53. or 54 or 55
57. 26 and 35 and 44 and 56

Table A1. *Quality assessment of the studies included in the systematic review*

First Author	Criteria													
	A	B	C	D	E	F	G	H	I	J	K	L	M	N
Duits [9]	1	0	0	1	1	NA	0	1	1	1	1	0	0	1
Lincoln [14]	1	0	0	1	0	NA	1	1	1	1	1	0	1	1
Visser-Keizer [21]	1	0	1	1	1	NA	1	1	1	0	1	0	1	1
Carlsson [7]	1	1	0	1	1	NA	1	1	1	0	0	0	0	0
Mok [17]	1	0	0	1	1	NA	1	1	1	0	0	0	0	0
Hochstenbach [10]	1	0	1	1	1	NA	1	1	1	0	0	0	1	1
Winkens [23]	1	0	1	1	1	NA	1	1	1	0	0	0	0	1
Wendel [22]	1	1	1	1	1	NA	1	1	1	0	1	0	1	1
Röding [20]	1	1	1	1	0	NA	1	1	1	0	1	0	0	1
Aben [6]	1	1	1	1	1	NA	1	1	1	1	1	0	0	1
McKevitt [16]	1	1	1	1	0	NA	1	1	1	0	1	0	0	1
Xiong [25]	1	0	0	1	1	NA	1	1	1	0	1	0	0	1
Narasimhalu [18]	1	0	1	1	1	NA	1	1	1	0	1	0	0	1
Pendlebury [19]	1	0	0	1	1	NA	1	1	1	0	1	0	0	1
Lamb [12]	1	0	1	1	1	NA	1	1	1	1	1	0	0	1
Davis [8]	1	0	1	1	0	NA	1	1	1	1	1	1	0	1
Keller [11]	0	0	1	1	0	NA	1	1	0	0	1	0	0	1
Liebermann [13]	1	0	1	1	1	NA	1	1	1	1	1	1	0	1
Martin [15]	1	0	1	1	1	NA	1	1	1	1	1	1	1	1
Winkens [24]	1	0	1	1	1	NA	1	1	1	1	1	1	0	1
Doyle [26]	1	0	0	1	0	0	0	1	1	1	1	0	0	1
van Heugten [28]	1	0	0	1	1	0	1	1	1	1	1	0	0	1
Wilz [29]	1	0	0	1	0	1	1	1	0	1	1	0	0	1
Tinson [27]	1	0	0	1	1	1	1	1	1	1	1	1	1	1
Doornhein [31]	1	0	0	1	0	NA	1	1	1	1	1	0	0	1
Aben [30]	1	0	1	1	1	NA	1	1	1	1	1	0	0	1
Total	25	5	15	26	18	2	24	26	24	14	22	5	6	24

1 = study meets criterion; 0 = study does not meet criterion.

Criteria: *A, Specific inclusion and exclusion criteria are reported; B, Participants are compared with non-participants with regard to baseline factors (e.g., sociodemographic and stroke characteristics); C, Time interval after stroke (i.e., mean and standard deviation or median and range) is reported; D, More than one sociodemographic variable (e.g., age, sex, education level) of the patient group is described; E, More than one clinical variable (e.g., type of stroke, lesion side, location, stroke severity) is reported; F, When SCC is evaluated in a longitudinal study, number or percentages of drop-outs are reported; G, The study is prospectively designed; H, The process of data collection is described sufficiently to make replication possible; I, SCC is one of the primary or secondary outcomes; J, SCC are evaluated by a psychometrically sound measure (i.e., published questionnaire or standardized interview rather than questions devised by the authors); K, At least one of the following variables is considered in relation to SCC: demographic characteristics, clinical characteristics, objective cognitive functioning, emotional complaints (e.g., depression or anxiety), fatigue, stress, personality characteristics or coping style; L, Post-stroke SCC are compared with those found in a non-stroke control sample; M, Agreement between self- and proxy-assessment of SCC is evaluated; N, Recognized statistical techniques are used to analyze the SCC data.*

Abbreviation: *NA, not applicable.*

CHAPTER 3

THE COMPLAINTS AFTER STROKE (COMPAS) STUDY:

PROTOCOL FOR A DUTCH COHORT STUDY ON POST-STROKE SUBJECTIVE COGNITIVE COMPLAINTS

BASED ON:

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ABSTRACT

Objective: Many studies have assessed post-stroke objective cognitive impairment, but only a few have evaluated patients' subjective cognitive complaints (SCC). Although these SCC are found to be common in both the early and chronic phase after stroke, knowledge about their risk factors, course over time, differences with healthy controls and their diagnostic relevance is limited. The aim of the COMPlaints After Stroke (COMPAS) study was therefore to determine the possible risk factors, prognosis, time course, and predictive value of SCC in the first 2 years after stroke.

Methods: A prospective cohort study was conducted in which patients were compared to non-stroke participants at 3, 6, 12, and 24 months after stroke. The intention was to recruit approximately 300 patients from the stroke units of two hospitals in The Netherlands, while 300 stroke-free participants were sought among the relatives (spouses excluded), social networks of participants and staff involved in the study. A wide range of subjective and objective variables was assessed in both groups using interviews, questionnaires, and neuropsychological assessment. The primary outcomes included SCC and objective cognitive impairment, whereas secondary outcomes were quality of life, subjective recovery and daily life functioning.

Ethics and dissemination: The study was carried out in agreement with the Declaration of Helsinki and the Medical Research Involving Human Subjects Act. The protocol has been approved by the medical ethics committees of the participating centers and all participants gave written informed consent. The results were published in peer-reviewed journals and disseminated to both the medical society and general public.

Discussion: The COMPAS study was, at time of development, the first which systematically evaluated post-stroke SCC in a prospective longitudinal design, while taking a wide range of subjective and objective variables into account. The results obtained can be used to accurately inform patients and their families and to develop patient-tailored intervention programs to ultimately improve stroke patient care.

INTRODUCTION

Post-stroke cognitive impairment is common after stroke and can be evaluated either objectively, using neuropsychological tests (i.e., objective cognitive performance, OCP), or subjectively, using interviews or self-report questionnaires (i.e., subjective cognitive complaints, SCC). Until now, the majority of the studies on post-stroke cognitive sequelae have focused on OCP without also evaluating patients' SCC. However, individuals' performances in test situations do not always correspond to those in daily life and vice versa [1, 2]. Evaluating one can therefore not be used to draw conclusions about the other. In a recent systematic review (Chapter 2 [3]) it was found that SCC are common in both the early and the chronic phase after stroke and that they tend to increase over time. The prevalence rates vary between 28.6% [4] and 92.0% [1] and complaints about memory, mental speed, and concentration are the most commonly reported (see Chapter 2 [3]). Furthermore, patients and their proxies generally show moderate agreement on the prevalence and severity of patients' SCC [5-10]. However, one of the main problems in most of the studies on post-stroke SCC is that there is no 'gold standard' to define and measure SCC, resulting in heterogenic findings. In our review (Chapter 2 [3]), we suggested that it is important to differentiate between two components of SCC, including: *content* of SCC (SCC-c) and *worry* about SCC (SCC-w). The first focuses on the specific cognitive difficulties respondents say they experience, while the second indicates whether participants find them to have an impact on daily life in terms of interference in activities of daily living (ADL), irritating and/or a source of concern. A few studies have made this distinction so far [2, 11, 12]. The majority of research on post-stroke SCC has evaluated SCC-c and not SCC-w (see Chapter 2 [3]), probably without being aware of the difference between these components.

Furthermore, it was found in the review (Chapter 2 [3]) that post-stroke SCC are inconsistently associated with demographic and clinical characteristics, current OCP and depressive symptoms, but that they may predict future cognitive decline and emotional well-being. However, most of the research on SCC after stroke carried out so far is limited in that: unvalidated methods for assessing SCC were used, no non-stroke control group was included, and the focus was on a specific subsample of stroke patients (e.g., home-living patients only), thereby impairing generalizability of the results (Chapter 2 [3]). While SCC are common among stroke survivors, knowledge about the following aspects is only limited or practically non-existent: the risk profile for developing SCC, their course over time, their impact on quality of life (QoL), subjective recovery and ADL, and their prognostic implications.

In the general non-stroke population however, SCC have been more frequently evaluated, in particular memory-related SCC reported by elderly [13, 14]. Factors found to be associated with these complaints include: demographic characteristics (higher age, women, low education), psychological distress, somatic complaints, personality traits (neuroticism in particular), and vascular risk factors [13-17].

Furthermore, they are thought to be clinically relevant in this population because of their association with current OCP (this link is not always found), their predictive value for future cognitive decline and a link with a reduced QoL and an increased health care consumption [13, 14, 18, 19]. Whether this also applies to post-stroke SCC, is unknown. More systematic research is therefore needed to gain further knowledge about SCC among stroke survivors, to be able to accurately inform patients and their relatives, to develop adequate treatment programs and ultimately improve post-stroke care.

The COMPlaints After Stroke (COMPAS) study was designed to address some of these questions. The four main aims of the study where:

- Determine the prevalence, profile and course over time of SCC-c and SCC-w.
- Identify the risk profile for reporting SCC.
- Evaluate the predictive value of SCC for future cognitive functioning.
- Determine the effect of SCC on ADL, subjective recovery and QoL.

Here the design and protocol of the COMPAS study is described. To the best of our knowledge, it was the first prospective cohort study of SCC in patients with a stroke, evaluating both patients and non-stroke controls, while at the same time a wide range of variables is taken into account.

METHODS

Design

A two-center, prospective cohort study of stroke patients and controls was performed. Between 2009 and 2014, patients were evaluated five times, starting at the clinical phase (T0), followed by an assessment at 3 months (T1), 6 months (T2), 1 year (T3), and 2 years (T4) after stroke. Non-stroke controls were seen at the same time intervals, starting at T1.

Study population

Stroke patients were recruited consecutively from the stroke units of Elisabeth-TweeSteden Hospital in Tilburg and the Maxima Medical Center in Veldhoven, The Netherlands. The control group consisted of a sample from the non-stroke general population and was recruited among the relatives and the social networks of participants and staff involved in the COMPAS study. Spouses of stroke patients were excluded from the control group since they are at risk of having physical, cognitive and psychosocial problems themselves due to the fact that their partner has suffered a stroke [20-22].

Inclusion criteria:

- Clinical diagnosis of a first or recurrent ischemic or hemorrhagic stroke (for patients only).
- At least 18 years old (no upper age limit).

Exclusion criteria:

- Premorbid health problems interfering with cognitive functioning, including for example cognitive decline (as defined by a score > 3.6 on the short version of the Informant Questionnaire on Cognitive Decline in the Elderly [23]).
- Life-threatening progressive diseases, including, but not limited to, for example cancer, kidney failure, progressive neurological conditions.
- A recent history of psychopathology, including for example suicide attempts, alcohol- or drug abuse, diagnosed personality or mood disorders.
- Severe communication difficulties, including for example insufficient understanding of the Dutch language, severe aphasia, blindness or deafness.

Procedure

Eligible patients received oral and written information about the study from their treating physician during the clinical phase (T0). Demographic and clinical characteristics were documented and patients were scheduled for the first assessment 3 months after stroke (T1), during which written informed consent was obtained for inclusion to be definite. Participants acknowledged that they had the intention to complete all assessments, but that they were allowed to end their participation at any time. For the follow-up assessments (T2 – T4), patients were informed by letter and telephone and invited to participate, after which an appointment was scheduled.

Potential controls received oral and written information about the study from the researcher after which they were asked to participate in the study. The rest of the procedure was the same as that for the patient group.

The assessments were administered in a standardized way by trained neuropsychologists and took place at the participating hospitals, or when this was not possible, at the participants' home or residence (e.g., rehabilitation center).

Measures

Tables 1 and 2 give an overview of the variables assessed and instruments used at each time point.

Outcomes

Primary outcomes of the COMPAS study where SCC and OCP. To measure SCC, two instruments were used, namely: the Dutch version of the Cognitive Failures Questionnaire (CFQ) [24, 25] and the Checklist for Cognitive and Emotional consequences following stroke (CLCE) [12]. The CFQ is a 25-item questionnaire designed by Broadbent et al. [24] to assess the occurrence of cognitive mistakes

experienced in daily life. As such, it is a measure of SCC-c. People have to rate the frequency of [25] cognitive mistakes on a 5-point Likert scale ranging from 0 (never) to 4 (very often). SCC-w was evaluated using 3 of the 4 items added to the Dutch CFQ by Ponds et al. [25]. Participants were asked to rate the degree to which they found their SCC-c (1) a hinder to daily life functioning, (2) a source of concern, and (3) annoying, on a 5-point Likert scale ranging from 1 (not at all) to 5 (extremely).

Table 1. *Primary and secondary outcomes in the COMPAS study*

		Instruments	T0	T1	T2	T3	T4
Primary outcomes							
	SCC	Cognitive Failures Questionnaire [24,25]		X	X	X	X
		Checklist for Cognitive and Emotional Consequences after stroke [12]		X	X	X	X
	OCP [28,29]						
	Global cognitive functioning	Mini-Mental State Examination		X		X	X
	Visual perception and construction	Rey Complex Figure Test – copy trial		X		X	X
	Mental speed / attention	Stroop Color word test - cards 1 and 2		X		X	X
		Digit Symbol-Coding		X		X	X
	Episodic memory	Rivermead Behavioral Memory Test		X		X	X
		Rey Complex Figure Test - immediate and delayed recall trials		X		X	X
		Verbal Paired Associates		X		X	X
	Working memory	Digit span Forward and Backward condition		X		X	X
	Language	Boston Naming Test - short version		X		X	X
	Executive functioning	Controlled Oral Word Association Test - F-A-S		X		X	X
		Category Fluency Test: animals and occupations		X		X	X
		Stroop Color Word Test - card 3		X		X	X
		Rule Shift Cards		X		X	X
		Zoo Map		X		X	X
	Fine motor dexterity	Purdue Pegboard		X		X	X
Secondary outcomes							
	Quality of Life	World health Organization Quality of Life Questionnaire – short form [30]		X		X	X
		World health Organization Quality of Life Questionnaire – OLD module [31]		X		X	X
	Subjective stroke recovery	Item 9 of Stroke Impact Scale [32]		P		P	P
	ADL						
	Basic ADL	Barthel index [34]	P	X	X	X	X
	Instrumental ADL	Frenchay Activities Index [35]		X	X	X	X

Abbreviations: *ADL, activities of daily living; C, control group only; OCP, objective cognitive performance; P, patient group only; SCC, subjective cognitive complaints; T0, clinical phase; T1, 3 months post-stroke; T2, 6 months post-stroke; T3, 1 year post-stroke; T4, 2 years post-stroke; X, instrument used in both patients and non-stroke controls.*

Table 2. *Possible determinants in the COMPAS study*

	Instruments	T0	T1	T2	T3	T4
Demographic variables	Age, sex, education, marital status, living situation, residence, employment status, hand preference	P	X	X	X	X
Clinical characteristics						
Stroke specific	Life-time history of stroke, type, side, classification according to the Oxford Community Stroke Project [40], severity within 24 hours after admission using the National Institutes of Health Stroke Scale [41], treatment, post-stroke complications, length of hospital stay, discharge destination	P				
General	Vascular risk factors, comorbidity (Cumulative Illness Rating Scale) [42]		X	X	X	X
	(re-) admissions to hospital, medication use, current participation in rehabilitation therapy					
Health status	12-Item Short Form Health Survey [43]		X		X	X
Premorbid status						
Cognitive decline	Informant Questionnaire on Cognitive Decline in the Elderly – short form [23]	P	C			
IQ-estimation	Dutch version National Adult Reading Test [44]		X			
Cognitive complaints	Self-made item: "in the previous months (before your stroke), have you experienced cognitive complaints?"	P	C			
Depressive complaints	Self-made item: in the previous months (before your stroke), have you experienced depressive complaints?"	P	C			
Anxiety complaints	Self-made item: in the previous months (before your stroke), have you experienced anxiety complaints?"	P	C			
Comorbid complaints						
Depressive complaints	Hospital Anxiety and Depression Scale – subscale Depression [45]		X	X	X	X
Anxiety complaints	Hospital Anxiety and Depression Scale – subscale Anxiety [45]		X	X	X	X
Perceived stress	Perceived Stress Scale, 4-item version [46]		X		X	X
Fatigue	Fatigue Assessment Scale [47]		X	X	X	X
Personal factors			X		X	X
Personality trait - neuroticism	Eysenck Personality Questionnaire Revised Short Scale – subscale Neuroticism [48]		X			
Personality trait - extraversion	Eysenck Personality Questionnaire Revised Short Scale – subscale Extraversion [48]		X			
Type D	Type D scale-14 [49]		X			
Coping style	Utrecht Coping List – 15-item version [50]		X			
Participants' awareness of SCC	Cognitive Failures Questionnaire completed by proxy		X	X	X	X
	Checklist for Cognitive and Emotional Consequences after stroke completed by proxy		X	X	X	X
Life events	Self-made item concerning the presence and impact of a positive or negative life event: "Last year, did something happen in your life which had a major impact on you? This may be something either pleasant or sad."		X		X	X

Abbreviations: *C, control group only; P, patient group only; SCC, subjective cognitive complaints; T0, clinical phase; T1, 3 months post-stroke; T2, 6 months post-stroke; T3,1 year post-stroke; T4, 2 years post-stroke; X, instrument used in both patients and controls*

The CLCE is a standardized clinical interview developed by van Heugten et al. [12] to identify the presence of cognitive and emotional problems after stroke. The instrument consists of 24 items, including: 13 cognitive, 9 emotional and 2 open items (the latter allowing for the addition of other problems not mentioned in the interview). Each item is rated on presence (i.e., the content component of SCC) and impact on daily life (i.e., the worry component of SCC) and scored as 0 (not present), 1 (presence uncertain), 2 (present, but no impact on daily life) or 3 (present and negatively affecting daily life) [11, 12]. In the studies presented in this dissertation, we focused on the 13 cognitive items from the CLCE. The emotional and open items were not analyzed because these topics were more thoroughly evaluated by other questionnaires used in the COMPAS study. Additional details regarding the CFQ and CLCE, including the individual items, psychometric properties and correlation matrix between the two instruments, are provided in the Appendix of this chapter.

OCP were evaluated using an extensive neuropsychological assessment covering multiple cognitive domains and containing both traditional (e.g., Rey Complex Figure Test [26]) and more ecologically valid tests (e.g., Rivermead Behavioral Memory Test [27]). Table 1 gives an overview of all OCP tests used. In Spreen and Straus [28] and Lezak et al. [29], a detailed description of each of the instruments is given.

Secondary outcomes included QoL, subjective recovery and ADL. Generic QoL was evaluated using the short version of the self-report World Health Organization Quality of Life Questionnaire (WHOQOL-Bref) [30] (26 items) and, because the majority of the study population was expected to be older than 60 years (i.e., the elderly population), the additional OLD module (WHOQOL-OLD) [31] comprising 24 items. While the first covers overall well-being on the domains 'physical', 'psychological', social relationships' and 'environment', the OLD module evaluates aspects of life which are specific to elderly, including: 'intimacy', 'sensory abilities', 'autonomy', 'activities in the past, present and future', 'social participation' and 'dying'.

Subjective recovery after stroke was determined by a single item from the Stroke Impact Scale [32], in which patients are asked to indicate on a scale ranging from 0 (no recovery) to 100 (full recovery) how much they feel they have recovered from their stroke.

ADL was assessed in basic activities, including self-care and mobility, using the Barthel Index [33, 34] (10 items) and more complex activities like housekeeping, hobbies and employment, using the Frenchay Activities Index [35] (15 items).

All instruments chosen are frequently used (inter)nationally in research and daily clinical practice dealing with stroke patients.

Possible determinants

Depending on the specific outcome considered, SCC, OCP, QoL, subjective recovery and ADL were either dependent or independent variables. A wide range of possible determinants were additionally taken into account, based on the literature on SCC in the general and stroke population. These included: demographic variables, clinical characteristics (those related to stroke included) and health status; premorbid status (i.e., cognitive decline, IQ, cognitive and emotional complaints); co-morbid psychological distress (i.e., anxiety, depression, perceived stress and fatigue); personal factors (i.e., coping style, personality traits and SCC awareness) and the occurrence and impact of positive and/or negative live events. See Table 2 for the specific variables assessed and instruments used in the COMPAS study. Table A2 in the Appendix of this chapter provides an overview of the instruments used in this dissertation.

Planned statistical analyses

Cross-sectional analyses were planned to be used to evaluate group differences at each of the individual time points (T1 to T4) and include: the Chi-square test for categorical variables, the Mann-Whitney U test for ordinal data and the Student t-test or (multivariate) analysis of variances ((M)ANOVA) for continuous variables. Furthermore, differences across the time points were, if possible, analyzed using multilevel analysis, which allows including all available data (i.e., also those from participants with partly missing values).

The course of SCC over time (T1 trough T4) was subsequently evaluated using paired samples t-tests (for two time points) and latent class growth analysis (when more than two time points were analyzed). It was also explored whether groups with different trajectories of SCC over the 2-year period can be distinguished and if so, what their characteristics are.

The predictive value of the determinants for the primary and secondary outcome measures (i.e., SCC, OCP, QoL, subjective recovery and ADL) at T3 and T4 were explored using multivariate regression analysis. Potential predictors were determined based on the SCC literature. In general, effects with a two-tailed $p < .05$ were considered statistically significant.

This dissertation presents the results of a subset of the research questions and analyses.

Sample size and power calculation

The sample size needed in the COMPAS study was calculated using the method for multilevel analysis according to Twisk [36]. Based on a high intra-individual correlation across the different time points (rho = 0.70), an alpha level of .05, and power of 0.80, there were 180 participants per group needed to be able to detect a small difference (at least 0.2 standard deviation) between the groups.

We expected about 40% drop-outs during the 2-year follow-up period due to comorbidity, refusal to continue participation or mortality. Therefore, we aimed to include 300 participants at baseline in each group in order to end up with the 180 per group needed.

A total of 211 patients and a comparison group of 155 individuals were recruited between October 2009 and August 2012. See Figure A1 in the Appendix of this Chapter for a flow chart of the participants assessend and analyzed in this dissertation.

ETHICS AND DISSEMINATION

Ethical considerations

The COMPAS study was conducted in accordance with the 'Helsinki Declaration' (Seoul revision, 2008) and the 'Medical Research Involving Human Subjects Act' (WMO). The study was non-invasive, imposed no risk on participants and its protocol has been approved by the medical ethical committees of the participating hospitals (i.e., Elisabeth-TweeSteden Hospital in Tilburg and the Maxima Medical Center in Veldhoven). It has been registered by the Central Committee on Research Involving Human Subjects (number NL31208.008.10). Furthermore, written informed consent was obtained from all participants.

Dissemination

The results obtained were disseminated to the scientific, medical and general public by publication in national and international peer-reviewed journals, as well as by presentations in conferences and meetings with clinicians dealing with stroke patients.

DISCUSSION

The COMPAS study is the first in which post-stroke SCC were systematically evaluated over time, while a wide range of subjective and objective variables in patients and controls was taken into account. While multiple studies have measured post-stroke OCP, only a few have also evaluated patients' SCC. Although these complaints are found to be common among stroke patients, knowledge about their risk factors, their course over time, differences with the non-stroke population, and their predictive value for future functioning is scarce (see Chapter 2 [3]).

Strong elements of the COMPAS study are its prospective design with multiple assessments during the first 2 years after stroke, and the extensive evaluations of both subjective and objective variables, which, based on the current literature, are potentially relevant to SCC after stroke. This makes it possible to determine a detailed risk profile for experiencing post-stroke SCC. Furthermore, the instruments chosen are widely accepted and frequently used in daily clinical practice dealing with stroke patients. Traditional neuropsychological and more ecologically valid tests (e.g., the Rivermead Behavioral Memory Test [27]) were used to evaluate OCP, making it possible to determine whether the ecological validity of tests affects the association between SCC and OCP. Also, a non-stroke comparison group was assessed at the same time points as the patients and was used as a reference group. This makes it possible to distinguish post-stroke SCC in their prevalence, profile and time course from, for example, factors which are associated with ageing.

A limitation of the study is that the most seriously affected patients with stroke are unable to participate, thereby reducing the possibility to generalize the results to the stroke population as a whole. However, the study differs from those already carried out in this field in that a broad selection of patients with stroke was included, not only those with a first-ever stroke or patients discharged home.

CONCLUSIONS

The COMPAS study has the potential to contribute to the knowledge on post-stroke SCC. Due to ageing of the population and health care improvements, the number of stroke survivors who will have to deal with post-stroke impairment will increase in the future, and the social and economic burden will rise accordingly [37-39]. Clinicians are frequently confronted with patients having SCC after their stroke, but the meaning and relevance of these SCC has yet to be determined. We aimed to elucidate the possible risk factors, prognosis and the predictive value of post-stroke SCC. This information can subsequently be applied by clinicians in daily practice in order to more accurately inform patients and their proxies and to treat SCC. The data may also prove useful in the future development of patient-tailored intervention programs to further optimize individual stroke patient-centered care, the ultimate aim of the COMPAS study.

REFERENCES

1] Lamb F, Anderson J, Saling M, Dewey H. Predictors of subjective cognitive complaint in post-acute older adult stroke patients. Arch Phys Med Rehabil. 2013;94:1747-1752.

2] Winkens I, Van Heugten CM, Fasotti L, Wade DT. Reliability and validity of two new instruments for measuring aspects of mental slowness in the daily lives of stroke patients. Neuropsychol Rehabil. 2009;19:64-85.

3] van Rijsbergen MW, Mark RE, de Kort PL, Sitskoorn MM. Subjective cognitive complaints after stroke: A systematic review. J Stroke Cerebrovasc Dis. 2014;23:408-420.

4] Pendlebury ST, Mariz J, Bull L, Mehta Z, Rothwell PM. MOCA, ACE-R, and MMSE versus the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery after TIA and Stroke. Stroke. 2012;43:464-469.

5] Hochstenbach J, Prigatano G, Mulder T. Patients' and relatives' reports of disturbances 9 months after stroke: Subjective changes in physical functioning, cognition, emotion, and behavior. Arch Phys Med Rehabil. 2005;86:1587-1593.

6] Lincoln NB, Tinson DJ. The relation between subjective and objective memory impairment after stroke. Br J Clin Psychol. 1989;28 (Pt 1):61-65.

7] Martin C, Dellatolas G, Viguier D, Willadino-Braga L, Deloche G. Subjective experience after stroke. Appl Neuropsychol. 2002;9:148-158.

8] Tinson DJ, Lincoln NB. Subjective memory impairment after stroke. Int Disabil Stud. 1987;9:6-9.

9] Visser-Keizer AC, Meyboom-de Jong B, Deelman BG, Berg IJ, Gerritsen MJ. Subjective changes in emotion, cognition and behaviour after stroke: Factors affecting the perception of patients and partners. J Clin Exp Neuropsychol. 2002;24:1032-1045.

10] Wendel K, Risberg J, Pessah-Rasmussen H, Stahl A, Iwarsson S. Long-term cognitive functional limitations post stroke: Objective assessment compared with self-evaluations and spouse reports. Int J Rehabil Res. 2008;31:231-239.

11] Duits A, Munnecom T, van Heugten C, van Oostenbrugge RJ. Cognitive complaints in the early phase after stroke are not indicative of cognitive impairment. J Neurol Neurosurg Psychiatry. 2008;79:143-146.

12] van Heugten C, Rasquin S, Winkens I, Beusmans G, Verhey F. Checklist for cognitive and emotional consequences following stroke (CLCE-24): Development, usability and quality of the self-report version. Clin Neurol Neurosurg. 2007;109:257-262.

13] Jonker C, Geerlings MI, Schmand B. Are memory complaints predictive for dementia? A review of clinical and population-based studies. Int J Geriatr Psychiatry. 2000;15:983-991.

14] Reid LM, Maclullich AM. Subjective memory complaints and cognitive impairment in older people. Dement Geriatr Cogn Disord. 2006;22:471-485.

15] Comijs HC, Deeg DJ, Dik MG, Twisk JW, Jonker C. Memory complaints; the association with psycho-affective and health problems and the role of personality characteristics. A 6-year follow-up study. J Affect Disord. 2002;72:157-165.

16] Jorm AF, Butterworth P, Anstey KJ, Christensen H, Easteal S, Maller J, et al. Memory complaints in a community sample aged 60-64 years: Associations with cognitive functioning, psychiatric symptoms, medical conditions, apoe genotype, hippocampus and amygdala volumes, and white-matter hyperintensities. Psychol Med. 2004;34:1495-1506.

17] Paradise MB, Glozier NS, Naismith SL, Davenport TA, Hickie IB. Subjective memory complaints, vascular risk factors and psychological distress in the middle-aged: A cross-sectional study. BMC Psychiatry. 2011;11:108.

18] Mol M, Carpay M, Ramakers I, Rozendaal N, Verhey F, Jolles J. The effect of perceived forgetfulness on quality of life in older adults; a qualitative review. Int J Geriatr Psychiatry. 2007;22:393-400.

19] Waldorff FB, Siersma V, Waldemar G. Association between subjective memory complaints and health care utilisation: A three-year follow up. BMC Geriatr. 2009;9:43.

20] Berg A, Palomaki H, Lonnqvist J, Lehtihalmes M, Kaste M. Depression among caregivers of stroke survivors. Stroke. 2005;36:639-643.

21] van Exel NJ, Koopmanschap MA, van den Berg B, Brouwer WB, van den Bos GA. Burden of informal caregiving for stroke patients. Identification of caregivers at risk of adverse health effects. Cerebrovasc Dis. 2005;19:11-17.

22] Rigby H, Gubitz G, Phillips S. A systematic review of caregiver burden following stroke. Int J Stroke. 2009;4:285-292.

23] de Jonghe JF, Schmand B, Ooms ME, Ribbe MW. [Abbreviated form of the informant questionnaire on cognitive decline in the elderly]. Tijdschr Gerontol Geriatr. 1997;28:224-229.

24] Broadbent DE, Cooper PF, FitzGerald P, Parkes KR. The cognitive failures questionnaire (CFQ) and its correlates. Br J Clin Psychol. 1982;21 (Pt 1):1-16.

25] Ponds R, van Boxtel M, Jolles J. [The 'cognitive failure questionnaire' as a measure of subjective cognitive functioning]. Tijdschrift voor neuropsychologie - diagnostiek, behandeling en onderzoek. 2006;1:37-45.

26] Osterrieth PA. [The test of copying a complex figure: A contribution to the study of perception and memory]. Arch Psychol. 1944;30:206-353.

27] Wilson B, Cockburn J, Baddeley A, Hiorns R. The development and validation of a test battery for detecting and monitoring everyday memory problems. J Clin Exp Neuropsychol. 1989;11:855-870.

28] Spreen O, Strauss E. A compendium of neuropsychological tests administration, norms and commentary. 2nd Ed. New York: Oxford University Press; 1998.

29] Lezak MD, Howieson DB, Loring DW. Neuropsychological Assessment. 4th Ed. New York, NY: Oxford University Press; 2004.

30. Skevington SM, Lotfy M, O'Connell KA. The World Health Organization's WHOQOL-BREF quality of life assessment: Psychometric properties and results of the international field trial. A report from the WHOQOL group. Qual Life Res. 2004;13:299-310.

31] Power M, Quinn K, Schmidt S. Development of the WHOQOL-OLD module. Qual Life Res. 2005;14:2197-2214.

32] Williams LS, Weinberger M, Harris LE, Clark DO, Biller J. Development of a stroke-specific quality of life scale. Stroke. 1999;30:1362-1369.

33] Mahoney FI, Barthel DW. Functional evaluation: The Barthel Index. Md State Med J. 1965;14:61-65.

34] de Haan R, Limburg M, Schuling J, Broeshart J, LJonkers L, van Zuylen P. [Clinimetric evaluation of the Barthel Index, a measure of limitations in activities of daily living]. Ned Tijdschr Geneeskd. 1993;137:917-921.

35] Holbrook M, Skilbeck CE. An activities index for use with stroke patients. Age Ageing. 1983;12:166-170.

36] Twisk JWR. Applied longitudinal data analysis for epidemiology. New York:

Cambridge University Press; 2003.
37] Donnan GA, Fisher M, Macleod M, Davis SM. Stroke. Lancet. 2008;371:1612-1623.
38] Strong K, Mathers C, Bonita R. Preventing stroke: Saving lives around the world. Lancet Neurol. 2007;6:182-187.
39] Di Carlo A. Human and economic burden of stroke. Age Ageing. 2009;38:4-5.
40] Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet. 1991;337:1521-1526.
41] Brott T, Adams HP, Jr., Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: A clinical examination scale. Stroke. 1989;20:864-870.
42] Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc. 1968;16:622-626.
43] Ware J, Jr., Kosinski M, Keller SD. A 12-item short-form health survey: Construction of scales and preliminary tests of reliability and validity. Med Care. 1996;34:220-233.
44] Schmand B, Bakker D, Saan R, Louman J. [The Dutch adult reading test: A measure of premorbid intelligence] Tijdschr Gerontol Geriatr. 1991;22:15-19.
45] Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand. 1983;67:361-370.
46] Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24:385-396.
47] Michielsen HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: The Fatigue Assessment Scale. J Psychosom Res. 2003;54:345-352.
48] Sanderman R, Arrindell WA, Ranchor A, Eysenck HJ, Eysenck SBG. [Measurement of personality traits using the Eysenck Personality Questionnaire: A manual]. Groningen: Noordelijk Centrum voor Gezondheidsvraagstukken, Rijksuniversiteit Groningen; 1995.
49] Denollet J. DS14: Standard assessment of negative affectivity, social inhibition, and type d personality. Psychosom Med. 2005;67:89-97.
50] Sanderman R, Ormel J. [The Utrecht Coping List (UCL): Validity and reliability]. Gedrag Gezond. 1992;20:32-37.
51] Barker-Collo SL, Feigin VL, Lawes CM, Parag V, Senior H. Attention deficits after incident stroke in the acute period: Frequency across types of attention and relationships to patient characteristics and functional outcomes. Top Stroke Rehabil. 2010;17:463-476.
52] Westerberg H, Jacobaeus H, Hirvikoski T, Clevberger P, Ostensson ML, Bartfai A, et al. Computerized working memory training after stroke--a pilot study. Brain Inj. 2007;21:21-29.
53] Bridger RS, Johnsen SA, Brasher K. Psychometric properties of the cognitive failures questionnaire. Ergonomics. 2013;56:1515-1524.

CHAPTER 3
APPENDIX

COGNITIVE FAILURES QUESTIONNAIRE (CFQ)

Total scores were computed (range 0-100) for participants who completed at least 22 items. For those with 3 or fewer missing items, missing values were imputed with the mean of the completed items.

The instrument is frequently used in research and clinical practice, also among stroke survivors [51, 52]. Psychometric properties are good (Chronbach's alpha ranging between 0.88 [25] and 0.93 [53], test-retest reliability r = 0.71) [53]. Although multiple factor structures have been proposed, a single-factor solution has been supported based on the inter-item correlations, the reliability of the items and the high internal consistency [53]. In the present study, Chronbach's alpha was 0.92 for the patient sample and 0.89 for the non-stroke group at the 3-months assessment.

Items of the Dutch version of the Cognitive Failures Questionnaire

De volgende 25 vragen gaan over kleine, alledaagse vergissingen die iedereen van tijd tot tijd maakt. Sommige van die vergissingen overkomen u waarschijnlijk wat vaker dan andere. Wij willen graag van u weten in hoeverre deze alledaagse vergissingen bij u zijn voorgekomen in de afgelopen 4 weken. Hieronder kunt u kiezen wat het beste bij u past. De mogelijkheden zijn: 'zeer vaak', 'vaak', 'af en toe', 'zelden' en 'nooit'.

1. Iets lezen en vlak daarna niet meer weten wat u nu gelezen hebt, zodat u het moet overlezen.
2. Vergeten waarom u naar een bepaald gedeelte van uw huis bent gelopen.
3. Wegwijzers over het hoofd zien.
4. Links en rechts verwarren bij het beschrijven van een route.
5. Per ongeluk tegen mensen opbotsen.
6. Niet meer weten of u het licht of het gas hebt uitgedaan, of de deur hebt afgesloten.
7. Niet luisteren naar de naam van een persoon op het moment dat deze persoon zich aan u voorstelt.
8. Iets er uitflappen en achteraf bedenken dat dit wel eens beledigend voor iemand zou kunnen zijn.
9. Niet merken dat iemand iets tegen u zegt als u met iets anders bezig bent.
10. Boos worden en daar later spijt van hebben.
11. Belangrijke brieven dagenlang onbeantwoord laten.
12. Vergeten welke straat u moet inslaan als u een route kiest die u goed kent, maar die u maar zelden gebruikt.
13. In een supermarkt niet kunnen vinden wat u zoekt terwijl het er wel is.
14. U plotseling afvragen of u een woord op de juiste manier gebruikt.
15. Moeite hebben met het nemen van een beslissing.
16. Afspraken vergeten.
17. Vergeten waar u iets hebt neergelegd, zoals een boek of een krant.
18. Per ongeluk iets weggooien dat u nodig hebt en bewaren wat u weg wilde gooien.
19. Dagdromen terwijl u eigenlijk naar iets of iemand zou moeten luisteren.
20. Namen van mensen vergeten.

21. Beginnen met iets maar het niet afmaken, omdat u ongemerkt met iets anders bent begonnen.
22. Niet op een woord kunnen komen terwijl het 'op het puntje van uw tong' ligt.
23. In een winkel vergeten wat u kwam kopen.
24. Dingen uit uw handen laten vallen.

In een gesprek niets meer weten om over te praten.

Extra items

1. Is het maken van deze alledaagse vergissingen in de afgelopen 5 jaar bij u toegenomen? (*Niet geanalyseerd in dit proefschrift*)

(1) helemaal niet toegenomen
(2) een klein beetje toegenomen
(3) matig toegenomen
(4) nogal sterk toegenomen
(5) zeer sterk toegenomen

2. Hoeveel hinder hebt u van het maken van deze vergissingen in het dagelijks leven?

(1) helemaal geen hinder
(2) zeer weinig hinder
(3) een beetje hinder
(4) veel hinder
(5) zeer veel hinder

3. In hoeverre maakt u zich zorgen over het maken van deze vergissingen in het dagelijks leven?

(1) helemaal geen zorgen
(2) zeer weinig zorgen
(3) een beetje zorgen
(4) veel zorgen
(5) zeer veel zorgen

4. Kunt u aangeven in hoeverre u zich ergert aan het maken van deze alledaagse vergissingen?

(1) het ergert mij helemaal niet
(2) het ergert mij een beetje
(3) het ergert mij matig
(4) het ergert mij nogal veel
(5) het ergert mij zeer veel

CHECKLIST FOR COGNITIVE AND EMOTIONAL CONSEQUENCES AFTER STROKE (CLCE)

The CLCE scores were analyzed in 3 ways:

- CLCE-content (CLCE-c) score: calculated by dichotomizing each item score into 'absent' (original item score 0) and 'present' (item scores 1 through 3) and summing them (score range CLCE-c = 0-13). This CLCE-c score represents the number of SCC present irrespective of whether these interfere with daily life (i.e., SCC-c). Higher scores indicate more SCC-c.
- CLCE-worry (CLCE-w) score: calculated by dichotomizing each item score into 'absence of interference' (original item scores 0 through 2) and 'presence of interference' (item scores 3) and summed over the 13 items (score range CLCE-w = 0-13). The CLCE-w score indicates the number of SCC having an impact on ADL (i.e., SCC-w). Higher scores indicate more SCC-w.
- CLCE-total (CLCE-t) cognitive score: calculated by summing the original 13 item scores referring to cognitive functioning (range 0-39). Higher scores indicate more SCC-c and/or more SCC-c having an impact on daily life. Results for the CLCE-t score were described only in Chapters 5 through 7.

The CLCE is found to be a valid instrument for screening self-reported cognitive and emotional problems among stroke survivors [12]. Van Heugten et al. [12] reported results on internal consistency, computed for the 22 standardized items, and found it to be good (Chronbach's alpha = 0.81). In our study the Chronbach's alpha, based on the 13 cognitive items, was 0.71 for the content component, 0.75 for the worry component, and 0.74 for the total cognitive score in the stroke sample (N = 208) at 3 months after stroke. For the comparison group (N = 155), the Chronbach's alpha's were 0.66, 0.63 and 0.66, respectively at the first assessment.

Items of the Checklist for Cognitive and Emotional Consequences after stroke (Dutch version)

Zijn onderstaande problemen sinds het CVA bij betrokkene aanwezig? Kies uit de antwoordmogelijkheden 'ja, het is erg hinderlijk', 'ja, maar niet hinderlijk', 'nee', 'twijfel'.

Cognitie:

1. Moeite om 2 dingen tegelijk te doen.
2. Moeite om de aandacht ergens bij te houden.
3. Moeite om alles bij te houden, langzamer geworden.
4. Moeite om nieuwe informatie te onthouden.
5. Moeite om informatie van langer geleden te onthouden, vergeetachtig.
6. Moeite om zelf initiatieven te nemen.
7. Moeite met het plannen en/of organiseren van dingen.
8. Moeite in concrete dagelijkse activiteiten uit te voeren (niet door verlamming).
9. Verminderd tot geen besef meer van tijd.
10. Verminderd tot geen besef meer van plaats, ruimte of persoon.

11. Geen aandacht meer voor een deel van het lichaam of de omgeving
12. Moeite om gesproken en/of geschreven taal te begrijpen.
13. Moeite om zelf te praten of te schrijven.

Emoties en gedrag:

14. Meer op zichzelf gericht, minder sociale contacten.
15. Irreële verwachtingen.
16. Sneller emotioneel, sneller huilen.
17. Sneller geïrriteerd, prikkelbaar.
18. Onverschillig, koel, minder uiten van gevoelens.
19. Ontremming, moeite met controle van gedrag.
20. Somber, neerslachtig, depressief.
21. Angstgevoelens.
22. Sneller en vaker moe.

Andere problemen die niet aan bod zijn gekomen:

23. ……
24. ……

Table A1. *Correlations (Pearson's r) between the CLCE and CFQ in the patient sample (N = 208) 3 months after stroke*

	CLCE-c	CLCE-w	CLCE-t	CFQ-c	CFQ-w hinder	CFQ-w concern	CFQ-w annoying
CLCE-c	1.0						
CLCE-w	0.83	1.0					
CLCE-t	0.98	0.92	1.0				
CFQ-c	0.55	0.54	0.57	1.0			
CFQ-w hinder	0.55	0.60	0.59	0.67	1.0		
CFQ-w concern	0.53	0.59	0.57	0.62	0.82	1.0	
CFQ-w annoying	0.50	0.57	0.55	0.60	0.75	0.80	1.0

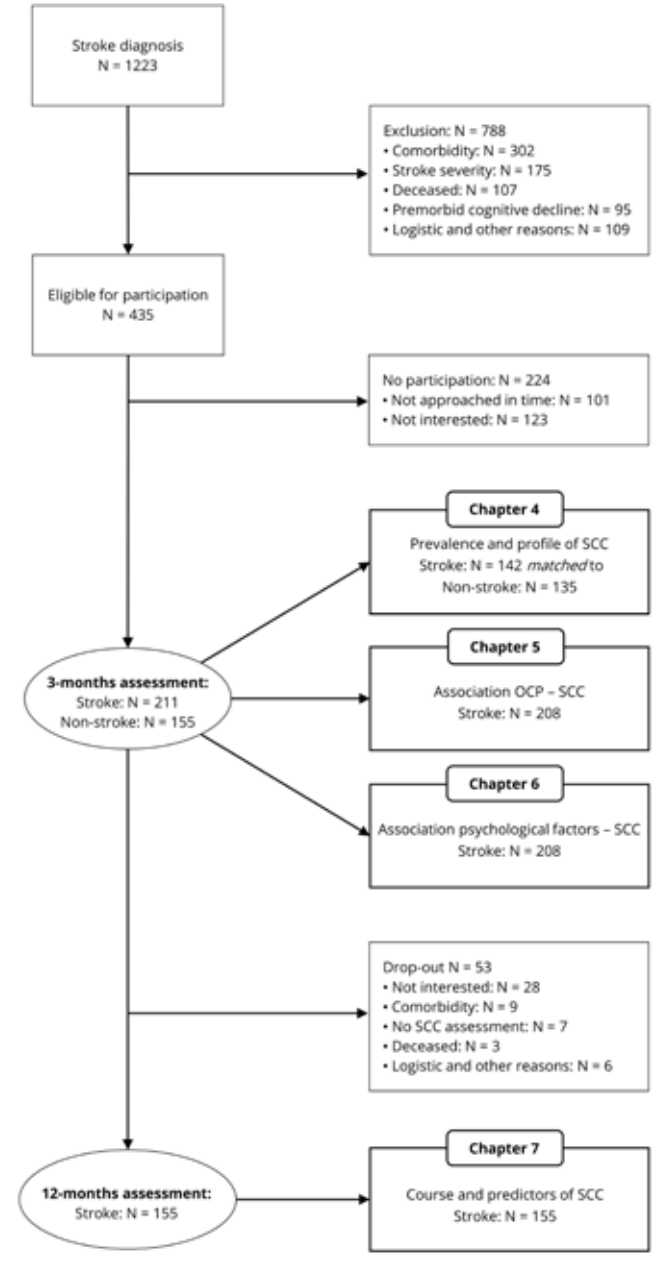
All p < .001 ***Abbreviations:*** *c, content; CFQ, Cognitive Failures Questionnaire; CLCE, Checklist for Cognitive and Emotional consequences after stroke; t, total; w, worry.*

Table A2. *Overview of the instruments (and their score range) used in this dissertation*

Instrument	Abbreviation	Range
Premorbid cognitive decline, Informant Questionnaire on Cognitive Decline in the Elderly – short form	IQCODE	1-5*
IQ estimation, Dutch version National Adult Reading Test	D-NART	66-130
Stroke severity, National Institutes of Health Stroke Scale	NIHSS	0-42*
Activities of daily living		
Barthel index	-	0-20
Frenchay Activities Index	FAI	0-45
Subjective cognitive complaints		
Cognitive Failures Questionnaire	CFQ	
Content	CFQ-c	0-100*
Worry (3 items)	CFQ-w	1-5*
Checklist for Cognitive and Emotional Consequences after stroke	CLCE	
Content	CLCE-c	0-13*
Worry	CLCE-w	0-13*
Total cognitive	CLCE-t	0-39*
Objective cognitive performance		
Mini-Mental State Examination	MMSE	0-30
Rey-Osterrieth Complex Figure Test	ROCF	
Time needed to copy	-	0-∞
Immediate and delayed recall	-	0-36
Stroop Color word test	Stroop	0-∞*
Digit Symbol-Coding	-	0-133
Rivermead Behavioral Memory Test	RBMT	
Verbal Paired Associates	VPA	
Immediate recall	-	0-32
Learning slope	-	-8 - +8
Delayed recall	-	0-8
Digit span forward and backward condition	-	0-30
Boston Naming Test - short version	-	0-87
Controlled Oral Word Association Test – FAS	COWA-F-A-S	0-∞
Category fluency test: animals and occupations	-	0-∞
Rule Shift Cards	-	0-4
Zoo Map	-	0-4
Psychological distress and fatigue		
Hospital Anxiety and Depression Scale	HADS	
Depression	HADS-D	0-21*
Anxiety	HADS-A	0-21*
Perceived Stress Scale, 4-item version	PSS-4	0-16*
Fatigue Assessment Scale	FAS	10-50*
Personality and coping		
Eysenck Personality Questionnaire Revised Short Scale	EPQ-RSS	
Neuroticism	-	0-12
Extraversion	-	0-12
Utrecht Coping List – 15 item version	UCL	
Avoidance	-	1-12
Active handling	-	1-20
Seeking social support	-	1-20
Palliative reaction	-	1-8

** High scores indicate a poor performance, a more severe stroke, or a high level of complaints. On the other instruments, high scores indicate a high level of independency, a good performance, or a high level of specific personality traits or coping styles.*

Figure A1. *Flow chart of the participants assessed and analyzed in Chapters 4 through 7*



Abbreviations: *OCP, objective cognitive performance; SCC, subjective cognitive complaints.*

CHAPTER 4

PREVALENCE AND PROFILE OF POST-STROKE SUBJECTIVE COGNITIVE COMPLAINTS

BASED ON:
Van Rijsbergen MWA, Mark RE, de Kort PLM, Sitskoorn MM
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ABSTRACT

Objective: Subjective cognitive complaints (SCC) are common after stroke, but detailed information on how SCC differ between patients with stroke versus stroke-free individuals is not available. We evaluated the prevalence and profile of the two SCC components (content and worry) in patients 3 months after stroke versus those found in a non-stroke sample, using both a generic and a stroke-specific instrument.

Methods: Using a cross-sectional design, 142 patients (mean age 61.7 ± 10.7 years, 60.6% men) were compared to 135 non-stroke participants (mean age 60.6 ± 10.1 years, 48.9% men). The groups were matched to each other on age, sex and estimated intelligence. SCC-content (SCC-c) and SCC-worry (SCC-w) were assessed using the Cognitive Failures Questionnaire (CFQ) and the Checklist for Cognitive and Emotional Consequences after stroke (CLCE) inventory. Univariate and multivariate linear (for continuous scores) and logistic (for dichotomous scores) regression analyses were used to explore differences between patients and stroke-free participants on both instruments.

Results: Based on the CLCE, patients reported more SCC-c (standardized β = 0.21, p = .001) and SCC-w (standardized β = 0.18, p = .02) than non-stroke participants in multivariate analyses. Profiles indicated that stroke was associated in particular with SCC in the domains of memory, attention, executive functioning and expressive language (for content), and with attention for SCC-w. In contrast, no group differences were found on SCC-c and SCC-w when assessed by the CFQ.

Conclusions: The prevalence and profile of SCC-c and SCC-w differ between patients and non-stroke individuals 3 months after stroke. The instrument used may, however, determine prevalence estimates. Stroke-specific inventories that differentiate between SCC-c and SCC-w are preferable when attempting to determine SCC after stroke.

INTRODUCTION

Subjective cognitive complaints (SCC) are common after stroke, with the prevalence ranging between 28.6%[1] and 92.0%[2]. Unfortunately, there is no consensus on the definition of SCC. In the systematic review (described in Chapter 2 [3]), SCC was defined defined SCC as a psychological construct with two different components, including: *content* (SCC-content; SCC-c) and *worry* (SCC-worry; SCC-w). Whereas SCC-c refers to what cognitive problems individuals report themselves, rather than actual objective test performance, SCC-w describes whether individuals in addition go on to report that their SCC-c have an impact on daily life in terms of interference in activities of daily living (ADL), irritation and/or worry. To the best of our knowledge, we are the first to explicitly make this distinction. We think it is important both for researchers and clinicians for at least two reasons. First, individuals who worry about their SCC-c may be more prone to psychological distress than individuals with SCC-c, but no SCC-w. Distress is linked to a lower quality of life [4] and probably a higher health care consumption. SCC-w may therefore be an important target for treatment. Second, the presence of SCC-c does not automatically imply that these are also perceived as SCC-w [5]. Researchers focusing on either SCC-c or SCC-w may therefore report different results and conclusions. Both components are however useful for gathering knowledge about SCC to improve care for individuals with SCC after stroke.

Most studies on post-stroke SCC have focused on SCC-c without also evaluating SCC-w [2, 6-10]. Findings are consistent: SCC-c on memory, mental speed and concentration are the most common [2, 6-9, 11]. However, SCC-c, especially those concerning memory, are also frequently reported by healthy adults [12]. Five of the six studies evaluating post-stroke SCC-c versus non-stroke controls showed that patients, assessed in the early [13, 14] or chronic phase [7, 10, 14, 15] after stroke, reported more SCC-c than controls (i.e., healthy adults [7, 10, 13, 15] or orthopedic patients [14]) on memory [7, 10, 13, 14], mental slowness [7, 15], attention [7] and executive function [7, 10]. Only Liebermann et al. [16] did not find such a difference among patients assessed 3 years post-stroke versus controls with a transient ischemic attack.

The other SCC component, SCC-w, has been examined after stroke in three studies [5, 15, 17]. Duits et al. [17] found that 73.7% of their sample assessed 5 weeks after stroke, reported at least one SCC-w, with worry about mental speed, attention and memory being the most prevalent. Aben et al. [5] focused on memory-related SCC-w, which they found among 74% of their sample assessed 4 years after stroke. Only Winkens et al. [15] compared post-stroke SCC-w between patients and controls and found that patients reported more SCC-w (about mental slowness) 7 months after their stroke.

Limitations of prior studies include: the absence of a control group [5, 17], the focus on either SCC-content [2, 6-10] or SCC-w [5, 17] instead of both, the evaluation of only one cognitive domain [5, 13-15], and/or the analysis of total SCC scores without exploring

individual items [5, 10, 15]. As a result, detailed information on if and how patients with a recent stroke differ from non-stroke samples on SCC-c and SCC-w on various cognitive domains is still missing. The aim of the current study was therefore to explore the prevalence and profile of SCC-c and SCC-w in patients (3 months after stroke) versus a non-stroke sample on multiple cognitive domains using both a generic and a stroke-specific instrument. Based on the literature, we expected to find more SCC-c and SCC-w in patients versus non-stroke individuals, especially on the domains memory, attention, mental speed and executive functioning.

METHODS

Participants

A subset of the original cohort who participated in the 3-months post-stroke assessment of the COMPlaints After Stroke (COMPAS) study (see Chapter 3 [18]) was analyzed. Inclusion criteria for COMPAS were: a first-ever or recurrent ischemic or hemorrhagic stroke (patients only) and at least 18 years old. Exclusion criteria were: premorbid health problems interfering with cognitive functioning (e.g., cognitive decline, as defined by a score > 3.6 on the short Informant Questionnaire on Cognitive Decline in the Elderly [19]), life-threatening progressive diseases (e.g., cancer or kidney failure), a recent history of psychopathology, severe communication difficulties, and/or (for the non-stroke sample only) being the spouse of a stroke patient. Patients were recruited consecutively from the stroke units of the Elisabeth-TweeSteden Hospital, Tilburg, and the Maxima Medical Center, Veldhoven, The Netherlands. Stroke-free participants were recruited among relatives and the social networks of participants and staff involved in the COMPAS study. All participants received detailed information before taking part and only those who gave written consent were included. The study was approved by the medical ethics committees of the hospitals mentioned above.

For the present study, the two groups were matched at group level on age, sex, and intelligence quotient (IQ) estimation (determined by the Dutch National Adult Reading Test, D-NART [20]), resulting in 142 patients and 135 non-stroke participants. See Figure 1 for a flow chart.

Materials

SCC-c and SCC-w were assessed using the Dutch Cognitive Failures Questionnaire (CFQ, a generic instrument) [21] and the Checklist for Cognitive and Emotional consequences after stroke (CLCE) [8] inventory (a stroke-specific instrument). Because prior studies have shown that SCC are linked to depression [2, 17], we also took into account depressive symptoms, measured using the depression subscale of the Hospital Anxiety and Depression Scale (HADS-D) [22].

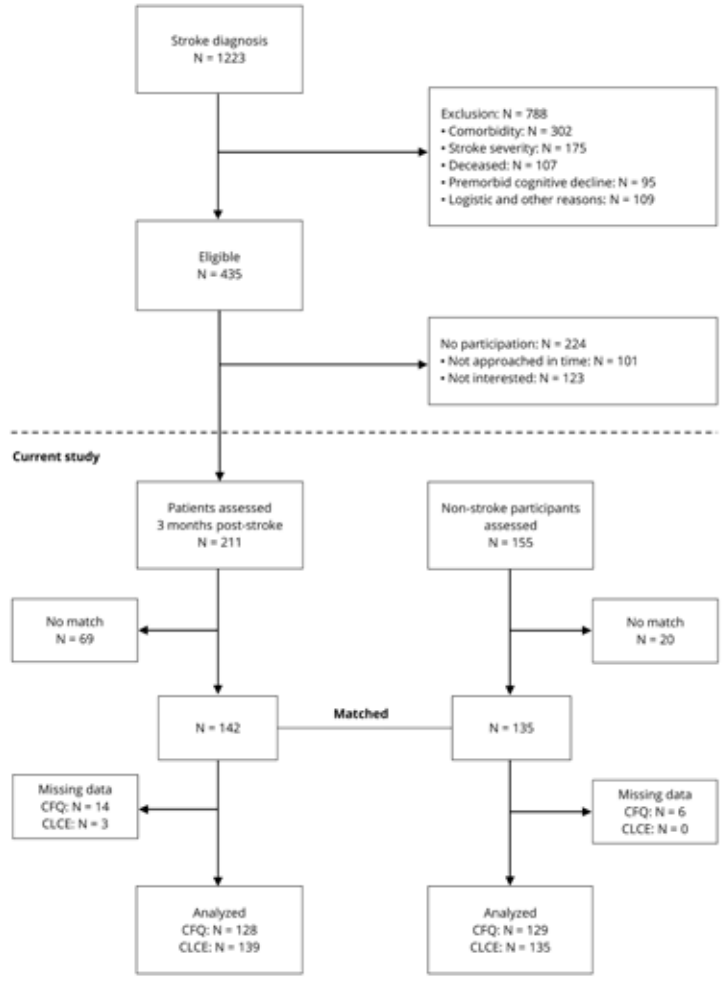
Cognitive Failures Questionnaire

SCC-content

The CFQ is a 25-item self-report questionnaire on which subjects rate the frequency of cognitive slips and errors (being an indication SCC-c) on a 5-point Likert scale ranging from 0 (never) to 4 (very often). Total scores (range: 0 – 100) were computed for participants who completed at least 22 of the 25 items [21]. For those with three or fewer missing items, the missing values were imputed with the mean of the completed items. Both total and item scores were analyzed to explore the prevalence and profile of SCC-c.

The instrument is frequently used, also in stroke patients [23, 24], and has good psychometric properties [25]. The internal consistency (Chronbach's alpha) of the CFQ in the present study was 0.91 for the total group, 0.92 for the patient sample and 0.89 for the non-stroke group.

Figure 1. *Flow chart*



Abbreviations: *CFQ, Cognitive Failures Questionnaire; CLCE, Checklist for Cognitive and Emotional consequences after stroke.*

SCC-worry

To measure SCC-w, subjects rated the degree to which they found their SCC-c (1) a hinder to daily life functioning, (2) a source of concern, and (3) annoying, each on a scale ranging from 1 (not at all) to 5 (extremely).

Checklist for Cognitive and Emotional consequences after stroke

SCC-content

The CLCE is a semi-structured interview evaluating post-stroke psychological changes. Thirteen of the 24 items assess self-reported cognitive problems and were used in the present study. Each item is scored as 0 (not present), 1 (presence uncertain), 2 (present, but no impact on daily life), or 3 (present and negatively affecting daily life). The prevalence and profile of SCC-c was evaluated by dichotomizing these scores into 1 'SCC-c present/doubtful' (original item scores 1 through 3) and 0 'SCC-c not present' (original item score 0). Total scores (range: 0-13) and individual items were analyzed.

The CLCE has been validated in stroke patients by Van Heugten et al. [8]. In the present study, the internal consistency (Chronbach's alpha) of the instrument was 0.73 for both the total group and the patient sample, and 0.67 for the non-stroke group.

SCC-worry

Original item scores were dichotomized into 1 'SCC-c negatively affecting daily life' (item score 3) and 0 'SCC-c present or doubtful, but not affecting daily life' (item score 0 through 2). Both item and total scores (range: 0–13) were considered.

Hospital Anxiety and Depression Scale

The depression subscale of the HADS is a self-report questionnaire consisting of 7 items. Subjects are asked to rate the presence of depressive symptoms on a 4-point Likert scale ranging from 0 to 3. Total scores were computed (range 0 – 21), with higher scores indicating greater severity of depressive symptoms. The HADS has been validated in stroke-survivor cohorts and is frequently used to screen for depression [26].

Procedure

Basic demographic information (age, sex) and stroke characteristics (type, side, stroke severity assessed by the National Institutes of Health Stroke Scale, NIHSS [27]) were determined and recorded by the treating neurologists during the acute phase (i.e., hospital stay). Three months after stroke, trained neuropsychologists estimated IQ (using the D-NART) and assessed SCC (using the CFQ and CLCE) and depressive symptoms (using the HADS-D). The CLCE, an interview, was always completed during the assessment itself, whereas the CFQ and HADS-D were typically filled in at home and returned by mail. Both patients and non-stroke participants followed the same assessment procedure.

Statistical Analysis

Differences between the patient and non-stroke comparison group on demographic variables were tested using independent samples t-tests (continuous variables) and Chi-square tests (categorical variables).

The association between 'group status' (i.e., stroke or non-stroke) and SCC was analyzed using linear regression analyses (for CFQ total SCC-c score and individual content and worry item scores, and for CLCE total SCC-c and -w scores) and logistic regression analyses (for dichotomous CLCE content and worry item scores). When significant results were obtained, multivariate regression models were used to evaluate whether the group effect remained after controlling for the effects of age, sex, IQ-estimation and depressive symptoms. Regression techniques were chosen for the analyses of both continuous and dichotomous scores to keep the analyses similar across the SCC instruments.

Two-sided p-values are reported and results were considered significant if $p < .05$. When multiple analyses were performed, Bonferroni correction (p/number of analyses) was applied to account for possible inflated Type I error. All analyses were performed using SPSS version 19.0 for Windows.

RESULTS

Sample characteristics

Table 1 depicts the demographic and stroke characteristics of the participants.

Table 2. *CFQ descriptives and the effect of group on CFQ total and item scores in univariate and multivariate linear regression analyses*

		Stroke	Non-stroke	Linear Regression Analyses	
		N = 128	N = 129	Univariate	Multivariate
		Mean ± SD	Mean ± SD	β (p-value)	β (p-value)
CFQ-c items					
1	Read something and have to read it again to remember it	1.7 ± 1.1	1.6 ± 0.8	0.01 (.93)	Not entered
2	Forget why you went from one part to the house to the other	1.1 ± 1.0	1.4 ± 0.8	**-0.15 (.02)** [a]	**-0.16 (.01)** [a]
3	Fail to notice signposts on the road	0.8 ± 0.8	1.2 ± 0.8	**-0.22 (<.001)** [b]	**-0.22 (.001)** [b]
4	Confuse right and left when giving directions	0.7 ± 1.0	0.8 ± 1.0	-0.06 (.38)	Not entered
5	Bump into people	0.5 ± 0.7	0.5 ± 0.6	0.02 (.81)	Not entered
6	Forget whether you have turned off a light or a fire or locked the door	0.9 ± 1.0	1.1 ± 0.8	-0.08 (.19)	Not entered
7	Fail to listen to people's names when meeting them	1.4 ± 1.1	1.6 ± 1.0	-0.11 (.09)	Not entered
8	Say something and realize afterwards that it might be taken as insulting	1.0 ± 0.8	1.2 ± 0.8	**-0.16 (.01)** [a]	**-0.23 (.001)** [b]
9	Fail to hear people speaking when doing something else	1.4 ± 1.0	1.4 ± 0.8	-0.02 (.75)	Not entered
10	Lose your temper and regret it	1.3 ± 1.0	1.4 ± 0.8	-0.04 (.58)	Not entered
11	Leave important letters unanswered for days	0.9 ± 1.0	0.6 ± 0.8	**0.18 (.003)** [a]	**0.15 (.03)** [a]
12	Forget which way to turn on a road you know but rarely use	0.6 ± 0.9	0.7 ± 0.7	-0.02 (.80)	Not entered
13	Fail to see what you want in a supermarket	1.0 ± 0.9	1.1 ± 0.8	-0.10 (.11)	Not entered
14	Wondering whether you have used a word correctly	1.2 ± 1.0	1.0 ± 0.8	0.12 (.05)	Not entered
15	Trouble making up your mind	1.1 ± 0.9	1.4 ± 0.8	**-0.19 (.003)** [a]	**-0.21 (.001)** [b]
16	Forgetting appointments	1.0 ± 0.9	0.9 ± 0.7	0.04 (.50)	Not entered
17	Forget where you put something like a newspaper or a book	1.4 ± 0.9	1.3 ± 0.8	0.02 (.71)	Not entered
18	Accidentally throw away the thing you want and keep what you meant to throw away	0.7 ± 0.7	0.6 ± 0.7	0.05 (.43)	Not entered
19	Daydreaming when ought to be listening to something	1.1 ± 0.9	1.3 ± 0.8	-0.07 (.24)	Not entered
20	Forgetting people's names	1.9 ± 1.1	2.1 ± 0.9	-0.12 (.06)	Not entered
21	Start doing one thing and get distracted into doing something else	1.1 ± 0.9	1.4 ± 0.9	**-0.18 (.004)** [a]	**-0.22 (.001)** [b]
22	Difficulty remembering something although it's "on the tip of your tongue"	2.0 ± 0.9	2.0 ± 0.7	0.01 (.88)	Not entered
23	Forget what you came to the shops to buy	0.7 ± 0.8	0.8 ± 0.7	-0.05 (.46)	Not entered
24	Drop things	0.9 ± 0.8	0.7 ± 0.7	0.12 (.06)	Not entered
25	Cannot think of anything to say	1.1 ± 0.9	1.1 ± 0.8	0.03 (.61)	Not entered
	Total score	27.4 ± 13.8	29.2 ± 10.3	-0.08 (.23)	Not entered

Table 2. *Continued*

	Stroke	Non-stroke	Linear Regression Analyses	
	N = 128	N = 129	Univariate	Multivariate
	Mean ± SD	Mean ± SD	β (p-value)	β (p-value)
CFQ-w items				
1 SCC-c are a hinder to daily life	2.1 ± 1.0	2.0 ± 0.8	0.07 (.30)	Not entered
2 SCC-c are a source of concern*	2.0 ± 0.9	1.9 ± 0.8	0.08 (.23)	Not entered
3 SCC-c are annoying*	1.9 ± 0.9	1.7 ± 0.7	0.12 (.05)	Not entered

*Each line represents 1 regression analysis with standardized β coefficients. In the multivariate regression analyses, the effect of group on SCC were evaluated after controlling for the effect of age, sex, IQ-estimation and depression score. * Due to missing values, the scores of 127 patients and 128 stroke-free individuals were analyzed.* **Signs:** *[a] p significant at < .05; [b] p significant at .05/25 ≤ .002 (univariate analyses) or at .05/6 ≤ .008 (multivariate analyses).* **Abbreviations**: *β, Standardized beta value; CFQ, Cognitive Failures Questionnaire, content, worry score; SCC, subjective cognitive complaints; SD, standard deviation.*

At the item level, group effects were found for 6 of the 25 items (items 2, 3, 8, 11, 15 and 21), of which 1 (item 3, fail to notice signposts) was significant at $p \leq .002$ (Bonferroni correction: .05/25 items). Multivariate analyses of the 6 items revealed that after controlling for the effects of age, sex, IQ-estimation and depression score, group differences were found on 4 of them (item 3, fail to notice signposts; 8, say something and realize afterwards that it might be insulting; 15, trouble making up your mind; and 21, getting distracted) at $p \leq .008$ (Bonferroni correction: .05/6 items). Table 2 displays specific patterns with, in general, non-stroke participants tending to report more SCC-c than patients. For the 3 items measuring SCC-w, no group effect was found (see Table 2).

Checklist for Cognitive and Emotional consequences after stroke

The total SCC-c score was computed for 139 patients and 135 non-stroke individuals (see Figure 1). One hundred twenty-four (89.2%) patients and 88 (65.2%) non-stroke participants reported at least one SCC-c. Group main effects were found for total SCC both in univariate and multivariate linear regression analyses (univariate: standardized $\beta = 0.29$, $p < .001$; multivariate: standardized $\beta = 0.21$, $p = .001$). Patients reported more SCC-c (mean 3.2 ± 2.4) than non-stroke participants (mean 1.9 ± 1.9).

At the item level, univariate logistic regression analyses showed that patients differed from non-stroke participants at $p < .05$ on 7 items (item 1, 2, 4, 6, 7, 11 and 12; see Table 3), of which 3 (item 1, multitasking; 2, attention; and 12, speaking or writing) reached significance at $p \leq .004$ (Bonferroni correction: .05/13 items). Multivariate logistic regression analyses on these 7 items showed that after controlling for the effects of age, sex, IQ-estimation and depressive symptoms, group differences were found at $p < .05$ on 5 items (item 1, 2, 6, 11 and 12), of which 3 (item 2, attention; 6, taking initiative; and 12, speaking or writing) reached significance after the Bonferroni correction (.05/7 items: $p \leq .007$) was applied (see Table 3).

Ninety-three (66.9%) patients and 55 (40.7%) non-stroke participants worried about at least one of their SCC-c (i.e., SCC-w). 'Group' had a significant effect on total number of SCC-w (univariate: standardized $\beta = 0.22$, $p < .001$; multivariate: standardized $\beta = 0.18$, $p = .02$). Patients reported more SCC-w (mean 2.2 ± 2.2) than non-stroke participants (mean 1.3 ± 1.5). At the item level, patients appeared to worry about different SCC-c than those in the non-stroke sample (see Table 3 for patterns). None were however significant after the Bonferroni correction (.05/13 items: $p \leq .004$) was applied.

Table 3. *Prevalence and profile of SCC (content and worry) on the CLCE and the effect of group on the item scores*

		CLCE-c				CLCE-w			
		Stroke	Non-stroke	Logistic Regression Analyses		Stroke	Non-stroke	Logistic regression Analyses	
		N = 139	N = 135	Univariate	Multivariate	N = 139	N = 135	Univariate	Multivariate
	Items	n (%)	n (%)	Odds Ratio (95% CI)	Odds Ratio (95% CI)	n (%)	n (%)	Odds Ratio (95% CI)	Odds Ratio (95% CI)
1	Doing 2 things at once	49 (35.3)	22 (16.3)	**2.8 (1.6 – 5.0)** [b]	**2.1 (1.1 – 4.0)** [a]	27 (19.4)	7 (5.2)	2.6 (0.9 – 7.6)	Not entered
2	Attending to things	59 (42.4)	33 (24.4)	**2.3 (1.4 – 3.8)** [b]	**2.5 (1.4 – 4.7)** [b]	42 (30.2)	16 (11.9)	**2.6 (1.1– 6.4)** [a]	**3.1 (1.1 – 8.9)** [a]
3	Have become slower	35 (25.2)	22 (16.3)	1.7 (0.9 – 3.1)	Not entered	20 (14.4)	11 (8.1)	1.3 (0.5 – 3.9)	Not entered
4	Remembering new information	61 (43.9)	43 (31.9)	**1.7 (1.0 – 2.7)** [a]	1.5 (0.9 – 2.7)	32 (23.0)	20 (14.8)	1.3 (0.6 – 2.8)	Not entered
5	Remembering old information	55 (39.6)	39 (28.9)	1.6 (0.9 – 2.7)	Not entered	32 (23.0)	16 (11.9)	2.0 (0.9 – 4.6)	Not entered
6	Taking initiative	50 (36.0)	29 (21.5)	**2.1 (1.2 – 3.5)** [a]	**2.5 (1.3 – 4.7)** [b]	32 (23.0)	14 (10.4)	1.9 (0.8 – 4.8)	Not entered
7	Planning and organizing	23 (16.5)	11 (8.1)	**2.2 (1.0 – 4.8)** [a]	Not entered	17 (12.2)	7 (5.2)	1.6 (0.3 – 7.6)	Not entered
8	Performing daily activities	4 (2.9)	0 (0)	NA	NA	3 (2.2)	NA	NA	NA
9	Perceiving time	18 (12.9)	9 (6.7)	2.1 (0.9 – 4.8)	Not entered	4 (2.9)	0 (0)	NA	NA
10	Orienting to places or persons	6 (4.3)	10 (7.4)	0.6 (0.2 – 1.6)	Not entered	5 (3.6)	8 (5.9)	NA	NA
11	Understanding language	15 (10.8)	5 (3.7)	**3.1 (1.1 – 8.9)** [a]	**3.6 (1.0 – 12.1)** [a]	10 (7.2)	3 (2.2)	1.3 (0.2 –10.7)	Not entered
12	Speaking or writing	66 (47.5)	30 (22.2)	**3.1 (1.9 – 5.3)** [b]	**3.2 (1.7 – 6.1)** [b]	38 (27.3)	12 (8.9)	2.0 (0.8 – 4.9)	Not entered
13	Attending to a part of the body or space	6 (4.3)	0 (0)	NA	NA	5 (3.6)	NA	NA	NA

In the multivariate regression analyses, the effect of group on SCC were evaluated after controlling for the effect of age, sex, D-NART (IQ-estimation) and HADS-D (depression score). ***Signs:*** *[a] p significant at < .05; [b] p significant at .05/13 ≤ .004 (univariate analyses) or at .05/7 ≤ .007 (multivariate analyses).* ***Abbreviations:*** *CI, confidence interval; CLCE, Checklist for Cognitive and Emotional consequences after stroke; NA, not applicable.*

DISCUSSION

We expected more SCC-c and SCC-w in patients tested at 3 months after stroke compared with a non-stroke sample, irrespective of the instrument used to measure it. We found, however, that this was only apparent when we used the stroke-specific and not the generic instrument. This finding may be explained by how the two instruments measure SCC. The CFQ is a generic instrument, filled out by individuals themselves and aimed at evaluating SCC-c which everyone experiences in daily life [21]. Items contain long sentences and answers have to be rated on a 5-point scale. We tested patients 3 months post-stroke and at this early stage of recovery, it is likely that many have not resumed their daily life activities to the pre-stroke level and that they are not as yet confronted by (many) cognitive failures. The CLCE on the other hand, is stroke-specific, is more sensitive to post-stroke SCC, is completed during a semi-structured interview and its questions are short and are answered with yes/no [8]. Asking for clarification on either the question or the response is easier to do during an interview than while filling out a questionnaire. Severe communication difficulties (for example due to aphasia) were an exclusion criterion for our sample, but it cannot be ruled out that for some participants the CFQ was too difficult. Future research may evaluate whether CFQ and CLCE results change when time after stroke passes and when both are given in interview form.

In agreement with previous studies on post-stroke SCC (see the review described in Chapter 2 [3]), we found SCC-c to be common (89.2% reported one or more SCC-c on the CLCE) and more prevalent among patients than among non-stroke participants on memory, attention and executive functioning (on the CLCE only). In contrast to the literature [7, 15], we observed no group differences on mental slowness. Differences in SCC-c on expressive language were prominent instead. These discrepancies in results across studies may be attributed to differences in samples evaluated, instruments used to assess SCC-c, and/or the time interval of assessment post-stroke. More research is needed to evaluate the effects of these factors on the prevalence and profile of post-stroke SCC.

The SCC-w prevalence (66.9% reported one or more SCC-w on the CLCE) is comparable with those reported by Duits et al. [17] and Aben et al. [5] (both approximately 74%). Although we found more SCC-w in total among patients than among the non-stroke sample on the CLCE, no group effects were seen on the item level (apart from 1 item on attention), that is, we did not replicate findings by Winkens et al. [15] on mental slowness. Possible reasons for not reporting worry or interference with daily life activities are: individuals use effective strategies to compensate for their SCC-c, thereby decreasing the burden [17], and/or patients may consider their SCC-c to be 'normal' and appropriate in the early phase after stroke or for their age [13, 14]. The assessment of interference with daily life activities versus worry related to specific cognitive domains requires further investigation. Nevertheless, the present findings require replication, not least because the

number of people reporting SCC-w was very small (i.e., ≤ 10 individuals on the items 8, 9, 10 and 13), possibly reducing the statistical power.

One of the limitations of this study is that there is no gold standard as yet on how to measure SCC. We used what is available in the literature, but both instruments have their shortcomings. The CFQ is frequently used and has established psychometric properties [25], but the SCC-w profile is not evaluated in detail. The CLCE is relatively new and although it has proven to be very promising [8], more research on the quality of the instrument is needed. We chose to use the CLCE because it is the only stroke-specific instrument available in the literature evaluating SCC on multiple cognitive domains, while also allowing us to differentiate what we refer to as SCC-c and SCC-w on the item level. Another limitation is that most of both our patient and non-stroke group were classified as having an average IQ, which reduces the generalizability to those with low or high IQ. Furthermore, while we both matched the groups on sex, age and IQ at the group level before conducting our analyses and also double checked using these variables as covariates, the sex differences (marginally more males in the patient group) cannot be completely eradicated. Most studies find that women in general report more SCC, which may partly explain our findings on the CFQ (no group differences due to more non-stroke females reporting SCC, bringing the scores of the two groups closer together). The present study was however not set up to explicitly investigate the influence of sex on the report of SCC. Lastly, we applied the Bonferroni method to correct for multiple testing. Although frequently used in research, this is a very stringent criterion and may have underestimated our findings.

Strong elements of the present study are: we are the first to clearly specify SCC by splitting it into two components and by measuring both on multiple cognitive domains; we used both a generic and a stroke-specific instrument to evaluate SCC; we analyzed both total and individual item scores to explore the profile of SCC-c and SCC-w; and we compared the results between patients and stroke-free individuals. We moreover did not only include patients discharged home (as most researchers in this field do; see Chapter 2 [3]), but included a heterogeneous stroke sample which helps the generalizability of our results. Stroke severity was relatively mild in our population (as assessed via the NIHSS), but recent research has suggested that cognitive burden in patients even with mild stroke, is high [28].

CONCLUSIONS

In conclusion, we have shown that content and worry are two different aspects of SCC and that both are common on multiple cognitive domains 3 months after stroke. The prevalence and profile of SCC-c and SCC-w differs between patients and non-stroke individuals, but how they differ depends on which instrument is used. We therefore think it is important that both researchers and clinicians differentiate between SCC-c and SCC-w and that a stroke-specific instrument may be preferable for the evaluation of the two SCC components at different time points after stroke. Future research may explore which factors are associated with post-stroke SCC-c and SCC-w (e.g., demographic and clinical characteristics, objective cognitive performance, mood, fatigue and/or personality traits), what their course is over time and whether they have prognostic value for future functioning. Ultimately, knowledge about what complaints patients have and what worries them will lead to improvements in stroke patient-centered care.

REFERENCES

1] Pendlebury ST, Mariz J, Bull L, Mehta Z, Rothwell PM. MOCA, ACE-R, and MMSE versus the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery after TIA and Stroke. Stroke. 2012;43:464-469.

2] Lamb F, Anderson J, Saling M, Dewey H. Predictors of subjective cognitive complaint in post-acute older adult stroke patients. Arch Phys Med Rehabil. 2013;94:1747-1752.

3] van Rijsbergen MW, Mark RE, de Kort PL, Sitskoorn MM. Subjective cognitive complaints after stroke: A systematic review. J Stroke Cerebrovasc Dis. 2014;23:408-420.

4] Teoh V, Sims J, Milgrom J. Psychosocial predictors of quality of life in a sample of community-dwelling stroke survivors: A longitudinal study. Top Stroke Rehabil. 2009;16:157-166.

5] Aben L, Ponds RW, Heijenbrok-Kal MH, Visser MM, Busschbach JJ, Ribbers GM. Memory complaints in chronic stroke patients are predicted by memory self-efficacy rather than memory capacity. Cerebrovasc Dis. 2011;31:566-572.

6] Hochstenbach J, Prigatano G, Mulder T. Patients' and relatives' reports of disturbances 9 months after stroke: Subjective changes in physical functioning, cognition, emotion, and behavior. Arch Phys Med Rehabil. 2005;86:1587-1593.

7] Martin C, Dellatolas G, Viguier D, Willadino-Braga L, Deloche G. Subjective experience after stroke. Appl Neuropsychol. 2002;9:148-158.

8] van Heugten C, Rasquin S, Winkens I, Beusmans G, Verhey F. Checklist for cognitive and emotional consequences following stroke (CLCE-24): Development, usability and quality of the self-report version. Clin Neurol Neurosurg. 2007;109:257-262.

9] Visser-Keizer AC, Meyboom-de Jong B, Deelman BG, Berg IJ, Gerritsen MJ. Subjective changes in emotion, cognition and behaviour after stroke: Factors affecting the perception of patients and partners. J Clin Exp Neuropsychol. 2002;24:1032-1045.

10] Maaijwee NA, Schaapsmeerders P, Rutten-Jacobs LC, Arntz RM, Schoonderwaldt HC, van Dijk EJ, et al. Subjective cognitive failures after stroke in young adults: Prevalent but not related to cognitive impairment. J Neurol. 2014.

11] Xiong YY, Wong A, Mok VC, Tang WK, Lam WW, Kwok TC, et al. Frequency and predictors of proxy-confirmed post-stroke cognitive complaints in lacunar stroke patients without major depression. Int J Geriatr Psychiatry. 2011;26:1144–1151.

12] Jonker C, Geerlings MI, Schmand B. Are memory complaints predictive for dementia? A review of clinical and population-based studies. Int J Geriatr Psychiatry. 2000;15:983-991.

13] Davis AM, Cockburn JM, Wade DT, Smith PT. A subjective memory assessment questionnaire for use with elderly people after stroke. Clinical Rehabilitation 1995;9:238-244.

14] Tinson DJ, Lincoln NB. Subjective memory impairment after stroke. Int Disabil Stud. 1987;9:6-9.

15] Winkens I, Van Heugten CM, Fasotti L, Wade DT. Reliability and validity of two new instruments for measuring aspects of mental slowness in the daily lives of stroke patients. Neuropsychol Rehabil. 2009;19:64-85.

16] Liebermann D, Ostendorf F, Kopp UA, Kraft A, Bohner G, Nabavi DG, et al. Subjective cognitive-affective status following thalamic stroke. J Neurol. 2013;260:386-396.

17] Duits A, Munnecom T, van Heugten C, van Oostenbrugge RJ. Cognitive complaints in the early phase after stroke are not indicative of cognitive impairment. J Neurol Neurosurg Psychiatry. 2008;79:143-146.

18] van Rijsbergen MW, Mark RE, de Kort PL, Sitskoorn MM. The complaints after stroke (compas) study: Protocol for a Dutch cohort study on poststroke subjective cognitive complaints. BMJ Open. 2013;3:e003599.

19] de Jonghe JF, Schmand B, Ooms ME, Ribbe MW. [Abbreviated form of the informant questionnaire on cognitive decline in the elderly]. Tijdschr Gerontol Geriatr. 1997;28:224-229.

20] Schmand B, Bakker D, Saan R, Louman J. [The Dutch adult reading test: A measure of premorbid intelligence]. Tijdschr Gerontol Geriatr. 1991;22:15-19.

21] Ponds R, van Boxtel M, Jolles J. [The 'cognitive failure questionnaire' as a measure of subjective cognitive functioning]. Tijdschrift voor neuropsychologie - diagnostiek, behandeling en onderzoek. 2006;1:37-45.

22] Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand. 1983;67:361-370.

23] Barker-Collo SL, Feigin VL, Lawes CM, Parag V, Senior H. Attention deficits after incident stroke in the acute period: Frequency across types of attention and relationships to patient characteristics and functional outcomes. Top Stroke Rehabil. 2010;17:463-476.

24] Westerberg H, Jacobaeus H, Hirvikoski T, Clevberger P, Ostensson ML, Bartfai A, et al. Computerized working memory training after stroke--a pilot study. Brain In. 2007;21:21-29.

25] Bridger RS, Johnsen SA, Brasher K. Psychometric properties of the cognitive failures questionnaire. Ergonomics. 2013;56:1515-1524.

26] Aben I, Verhey F, Lousberg R, Lodder J, Honig A. Validity of the beck depression inventory, hospital anxiety and depression scale, SCL-90, and hamilton depression rating scale as screening instruments for depression in stroke patients. Psychosomatics. 2002;43:386-393.

27] Brott T, Adams HP, Jr., Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: A clinical examination scale. Stroke. 1989;20:864-870.

28] Kauranen T, Laari S, Turunen K, Mustanoja S, Baumann P, Poutiainen E. The cognitive burden of stroke emerges even with an intact NIH Stroke Scale score: A cohort study. J Neurol Neurosurg Psychiatry. 2014;85:295-299.

CHAPTER 5

THE ROLE OF OBJECTIVE COGNITIVE DYSFUNCTION IN SUBJECTIVE COGNITIVE COMPLAINTS AFTER STROKE

BASED ON:

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ABSTRACT

Objective: Objective cognitive performance (OCP) is often impaired in patients post-stroke, but the consequences of OCP for patient-reported subjective cognitive complaints (SCC) are poorly understood. We performed a detailed analysis on the association between post-stroke OCP and SCC to increase knowledge on this topic.

Methods: Assessments of OCP and SCC were obtained in 208 patients (mean age 64.9 ± 12.4 years; 65.9% men) 3 months after stroke (mean 3.3 ± 0.5 months). OCP was evaluated using conventional and ecologically valid neuropsychological tests. Levels of SCC were measured using the Checklist for Cognitive and Emotional consequences following stroke (CLCE) inventory. Multivariate hierarchical regression analyses were used to evaluate the association of OCP with CLCE scores adjusting for age, sex and estimated intelligence. Analyses were performed to examine the global extent of OCP dysfunction (based on the total number of impaired neuropsychological tests, i.e., the objective cognitive impairment index) and for each OCP test separately using the raw neuropsychological (sub)test scores.

Results: The objective cognitive impairment index for global OCP was positively correlated with the CLCE score (Spearman's rho = 0.22, p = .003), which remained significant in multivariate adjusted models (standardized β = 0.25, p = .01). Results for the separate neuropsychological tests indicated that only one task (the ecologically valid Rivermead Behavioral Memory Test) was independently associated with the CLCE in multivariate adjusted models (standardized β = -0.34, p < .001).

Conclusions: Objective neuropsychological test performance, as measured by the global dysfunction index or an ecologically valid memory task, was associated with SCC. These data suggest that cumulative deficits in multiple cognitive domains contribute to subjectively experienced poor cognitive abilities in daily life in patients 3 months after stroke.

INTRODUCTION

Neuropsychological tests, measuring various domains of objective cognitive performance (OCP), play a critical role in the clinical evaluation of cognitive functioning in patients who have experienced a stroke. Impairments are consistently shown in both the early and chronic post-stroke phases, although the prevalence estimates vary substantially across studies (ranging between 10% and 82%) [1]. Poor performance is primarily seen on tasks requiring mental speed, attention, memory and executive functioning [1, 2]. In addition to OCP defects, patient-reported subjective cognitive complaints (SCC) are prevalent after stroke (Chapter 2 [3]). Estimates range from 28.6% [4] to 92.0% [5] and the most commonly reported SCC are in the domains of mental speed, concentration and memory (see the systematic review in Chapter 2 [3]). Recent evidence indicates that the 'objective' neuropsychological measures do not consistently correspond with patients' SCC, but that both are important aspects of the clinical management of patients after stroke [5-7].

The nature and magnitude of the association between post-stroke OCP and SCC vary across studies with positive [8-10] and null findings [6, 7, 11]. In studies exploring the association between post-stroke OCP and SCC on specific cognitive domains, such as memory, the findings are also inconsistent, with positive [12] but also non-significant [13] findings. Similar discrepancies have been found in the domain of executive functioning [7, 10].

The inconsistent results regarding the correspondence between post-stroke OCP and SCC may at least partly be accounted for by the ecological validity of the neuropsychological test utilized to assess OCP. When ecologically valid neuropsychological tests are used, correlations between OCP and SCC may be higher because such valid instruments closely resemble real life cognitive tasks [12, 14]. Most post-stroke studies, however, have used conventional neuropsychological measures of OCP [4, 7, 15-17]. It is also possible that the range of cognitive deficits is an important determinant of the association between OCP and SCC (i.e., the more domains of objective dysfunction there are, the more likely patients will also experience SCC).

In addition, the current literature on post-stroke SCC is complicated by the lack of consensus on the definition of SCC and its critical components (see Chapter 2 [3]). Based on our systematic review of studies on SCC after stroke (Chapter 2 [3]) two components of SCC were identified: a primary *content* component referring to the nature of cognitive difficulties (i.e., the type and number of different complaints), and a *worry* component (i.e., the extent to which individuals experience daily life interference of their specific content-related SCC).

In the present study, we examined whether OCP based on standardized neuropsychological examination is associated with patient-reported SCC at 3 months after stroke. The association between OCP and SCC was evaluated in two ways: (i) at the global level by using composite (sum) scores for both OCP and SCC and (ii) at the level of separate OCP domains, using separate neuropsychological tests comprising standard instruments as well as ecologically valid tests that closely resemble daily life cognitive activities. We also determined whether OCP is differentially related to the content of SCC (i.e., the nature of SCC) versus the impact of SCC in terms of worry and hindrance.

METHODS

Design and procedure

Patients were evaluated at 3 months (mean 3.3 ± 0.5 months) post-stroke as part of the COMplaints After Stroke (COMPAS) study. The design and procedures of the COMPAS study have been described in Chapter 3 [18]. Between October 2009 and August 2012, patients were recruited from the Elisabeth-TweeSteden Hospital in Tilburg and the Maxima Medical Center in Veldhoven, The Netherlands. The medical ethics committees of these hospitals approved the protocol and written informed consent was obtained from all participants.

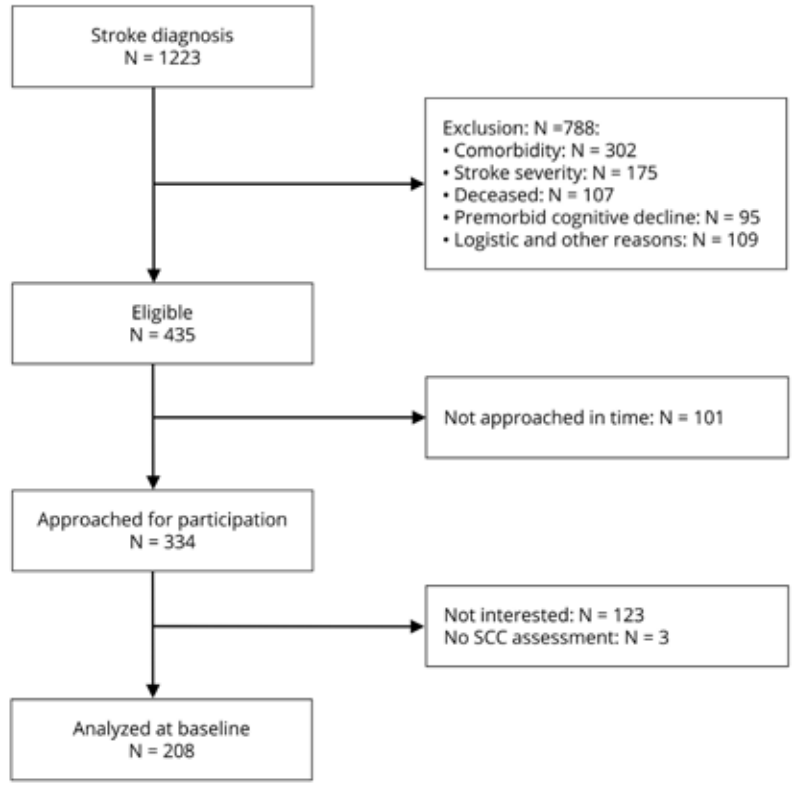
Stroke characteristics (type, side and stroke severity, based on the National Institutes of Health Stroke Scale, NIHSS [19]) were recorded by the treating neurologists during hospitalization for stroke. Assessment of OCP and SCC were performed by trained neuropsychologists at 3 months after stroke.

Participants

Patients with a clinical diagnosis of stroke (either ischemic or hemorrhagic, first-ever or recurrent) and aged ≥ 18 years were eligible for this study. Exclusion criteria were: premorbid health problems interfering with cognitive functioning (e.g., cognitive decline, as defined by a score > 3.6 on the short version of the Informant Questionnaire on Cognitive Decline in the Elderly [20]), life-threatening progressive diseases (e.g., cancer or kidney failure), a recent history of psychopathology and/or severe communication difficulties.

A total of 435 patients were eligible, of whom 208 (47.8%) agreed to participate and had an SCC assessment (see Figure 1). Non-participants (i.e., patients who were not interested, N = 123), those who could not be approached in time for the assessment (N = 101), and those who had no SCC assessment (N = 3), did not differ from participants in stroke type (93.0% versus 94.7% had an ischemic stroke, $\chi^2(1) = 0.58$, p = .45), but they more often had a left-sided lesion (56.5% versus 42.9%, $\chi^2(1) = 7.1$, p = .01) and were less severely affected by their stroke at time of admission (median NIHSS score = 2, interquartile range (IQR) = 1 - 4 versus 3, IQR = 2 - 5; U = 18088.5, p = .03). Non-participants were also older (69.6 ± 12.4 versus 64.7 ± 12.4 years, $t(433) = -4.1$, p < .001) and were more often female (44.5% versus 34.1%, $\chi^2(1) = 4.9$, p = .03).

Figure 1. *Flow-chart of the study population*



Abbreviation: *SCC, subjective cognitive complaints.*

Neuropsychological assessment of objective cognitive performance

Standard neuropsychological tests were used to assess OCP. In addition to the Mini-Mental State Examination (MMSE), which was used as an indication of general cognitive performance, five specific cognitive domains were evaluated: (i) mental speed and attention [Stroop Color Word Test – cards I (reading) and II (naming); Digit Symbol Coding], (ii) memory [Digit span; Rey-Osterrieth Complex Figure Test (ROCF) – immediate and delayed recall; Verbal Paired Associates (VPA) – immediate recall, learning curve, delayed recall] (iii) executive function [Stroop Color Word Test – card III and the interference, i.e., score time card III – 0.5 (time card I + II) / 0.5 (time card I + II)], (iv) expressive language [Boston Naming Test; Category Fluency – total number of correct animals and occupations; Controlled Oral Word Association Test F-A-S (COWA-F-A-S) – total number of correct words], and (v) visuospatial functioning (ROCF – time needed to copy and the copy score). A second set of OCP neuropsychological tests was included because of their high ecological validity: the Rivermead Behavioral Memory Test (RBTM, memory domain) and the Rule Shift Cards and Zoo Map Test (both from the Behavioral Assessment of the Dysexecutive Syndrome, executive functioning domain). A detailed description of these OCP instruments can be found in Spreen and Straus [21] and Lezak et al. [22].

Neuropsychological test results were analyzed in two ways. First, individual test scores were dichotomized into 'impaired' and 'not impaired' based on established norm-based cut-off values. Similar to procedures described by Davis et al. [23] and Silk-Eglit et al. [24], the total number (i.e., sum) of impaired (sub)test scores resulted in the objective cognitive impairment (OCI) index (range 0-20). Second, raw neuropsychological (sub)test scores were used to explore the separate components of OCP.

Subjective cognitive complaints

The presence (i.e., number and nature) of SCC (SCC-content; SCC-c) and interference with daily life (SCC-worry; SCC-w) were assessed using the Checklist for Cognitive and Emotional consequences following stroke (CLCE) [16] inventory. The CLCE is a semi-structured interview evaluating subjective cognitive, emotional and behavioral changes after stroke. Thirteen of the 24 items focus on self-reported cognitive problems and were used in the present study. The items referring to affect and mood were not included (see also Duits et al. [6] and Nijsse et al. [25]). Each item was scored on presence and interference in daily life: 0 (SCC not present), 1 (presence uncertain), 2 (present, but not affecting daily life), 3 (present and negatively affecting daily life). The CLCE has good psychometric properties (Chronbach's alpha = 0.81 based on the standardized 22 items [16]; in the present study Chronbach's alpha = 0.79).

The primary SCC measure was the CLCE-content (CLCE-c) score, defined as the number of SCC present irrespective of whether these interfered with daily life (see also Chapter 4 [26]). Specifically, this CLCE-c score was calculated by dichotomizing each item score into 'absent' (original item score 0) and 'present' (item score 1 through 3) and summing the items (score range CLCE-c score = 0-13). The internal consistency of this CLCE-c score was adequate (Chronbach's alpha = 0.71).

Exploratory analyses were conducted for: (i) the CLCE-w score, (ii) CLCE-total (CLCE-t) cognitive score (sum of the 13 item scores 0-3; range, 0-39), and (iii) each of the CLCE items separately. The CLCE-w score was calculated by summing items with score 3 (i.e., SCC present and negatively affecting daily life) over the 13 items (CLCE-w score range, 0-13). This approach to quantifying the CLCE-w component as an index of the impact of SCC has been used previously [6, 25]. The internal consistency (Chronbach's alpha) of this CLCE-w score was 0.75.

Demographic and clinical measures

Age, sex and estimates of intelligence quotient (IQ), based on the Dutch version of the National Adult Reading Test (D-NART [27]), were included as covariates. Additional measures included premorbid cognitive functioning assessed using the IQCODE. Medical records were reviewed for stroke type, lateralization, and NIHSS score.

Statistical analysis

Data are presented as mean ± standard deviation or frequencies and % as appropriate. The association between OCP and SCC was evaluated by (i) examining the global OCP dysfunction level using the total OCI-index and CLCE scores, and (ii) by investigating separate OCP components using the individual neuropsychological (sub)tests. Bivariate associations of the OCI-index and the neuropsychological (sub)tests with the CLCE scores were examined using non-parametric Spearman correlations (rho). Multiple linear regression analyses were used to examine whether the association between OCP indices (i.e., total OCI-index score and individual neuropsychological test scores) with CLCE-c scores were independent of covariates (age, sex and IQ). Specifically, age, sex, and IQ were included in the first block and OCP (either the OCI-index or the individual neuropsychological test scores) in the second block. Standardized regression coefficients (β) were used to indicate the strength of the associations. The multiple regression models were used to examine the joint association between the multiple OCP measures with SCC and minimize statistical Type I error related to multiple comparisons. Assumptions for multiple linear regression were examined by evaluating the plots of the residual scores and multicollinearity indices (variance inflation factor). To minimize bias related to multicollinearity of related neuropsychological tests (i.e., when the correlations between two neuropsychological tests was ≥ 0.70), only one neuropsychological test (the one with the highest bivariate correlation with the CLCE score) was used in the multivariate model.

The exploratory per-item analyses used logistic regression models with the dichotomous CLCE item scores as outcome measure (data presented as odds ratios and 95% confidence intervals).

In addition to the CLCE-c score (i.e., the primary outcome measure), we also explored the associations between OCP with the CLCE-w and CLCE-t score using the same procedure as described above.

Two-sided p-values are reported and a p-value < .05 was considered to indicate statistical significance. Correction for multiple testing was accomplished by first examining overall MANCOVA effects or model R^2 and component measures were only examined if the overall multivariate effect was significant. All statistical analyses were performed using SPSS 22.0 software for Windows.

RESULTS

Characteristics of participants

Basic demographic and clinical characteristics are shown in Table 1. Most patients had a first-ever stroke of the ischemic type. Stroke severity was relatively mild (median NIHSS score = 3 out of 42 points) and most of the patients were discharged to their home and only a few to a rehabilitation facility. Global cognitive functioning (MMSE total score) was 28.3 ± 1.7 and 4 patients (1.9%) had an abnormal MMSE score < 24 [28].

Table 1. *Demographic and stroke characteristics of the study sample (N = 208)*

Variable	
Age in years	64.9 ± 12.4
Males	137 (65.9)
D-NART, IQ-estimation	95.4 ± 12.9
IQCODE, premorbid cognitive decline [a]	3.1 ± 0.2
Follow-up duration (months after stroke)	3.3 ± 0.5
NIHSS, stroke severity at admission, median [Q1 – Q3]	3 [2 – 5]
First-ever stroke	187 (89.9)
Ischemic stroke	197 (94.7)
Lesion side	
Left	78 (37.5)
Right	104 (50.0)
Not differentiated	26 (12.5)
Discharge destination	
Home	179 (86.1)
Clinical rehabilitation	29 (13.9)

Data are given as mean ± standard deviation and n (%).[a] Due to missing values, scores are based on 130 patients. ***Abbreviations:*** *D-NART, Dutch version of the National Adult Reading Test; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; NIHSS, National Institutes of Health Stroke Scale; Q1, first quartile; Q3, third quartile.*

The raw scores and the number of participants scoring below norm-based cut-off values on the individual neuropsychological tests are shown in Table 2. The highest frequency of below-threshold performance was observed for the RBMT (72.1%), the Zoo Map test (61.0%) and the COWA-F-A-S test (60.7%). On average, on 6 tests, the scores were below the cut-off value (OCI-index mean = 5.9 ± 3.7).

Table 2. *Objective cognitive performance: raw scores and number of participants scoring below established norm-based cut-off values*

	n [a]	Mean ± SD	Impaired, n (%)
Mental speed/attention			
Stroop I (reading) (time in sec.) [b]	203	56.3 ± 15.4	98 (48.3)
Stroop II (naming) (time in sec.) [b]	202	69.7 ± 17.7	60 (29.7)
Digit-symbol coding (total correct)	207	48.2 ± 17.5	85 (41.1)
Memory			
Digit span (total score)	206	13.0 ± 3.4	48 (23.3)
RBMT (total profile score)	204	18.8 ± 4.0	147 (72.1)
ROCF (immediate recall)	203	15.5 ± 7.9	55 (27.1)
ROCF (delayed recall)	204	15.2 ± 7.6	58 (28.4)
VPA (immediate recall, total correct)	195	12.3 ± 7.6	35 (17.9)
VPA (learning slope)	195	3.6 ± 2.1	10 (5.1)
VPA (delayed recall, total correct)	195	4.1 ± 2.6	33 (16.9)
Executive functioning			
Stroop III (interference) (time in sec.) [b]	200	126.1 ± 49.5	52 (26.0)
Stroop (interference score) [b]	200	1.0 ± 0.5	25 (12.5)
Rule Shift Cards (profile score)	205	3.0 ± 1.1	48 (23.4)
Zoo Map (profile score)	200	2.1 ± 1.2	122 (61.0)
Expressive language			
Category fluency (total correct)	206	33.4 ± 10.7	70 (34.0)
COWA-F-A-S (total correct)	206	23.2 ± 10.5	125 (60.7)
Boston Naming Test (total correct)	208	70.2 ± 13.5	80 (38.5)
Visuospatial functioning			
ROCF (time needed to copy)	204	209.3 ± 110.9	14 (6.9)
ROCF (copy score)	205	29.8 ± 5.9	78 (38.0)

[a] Sample sizes (n) are based on the number of participants who completed the neuropsychological test. [b] Lower scores indicate better performances, while on the other tests the opposite is true.

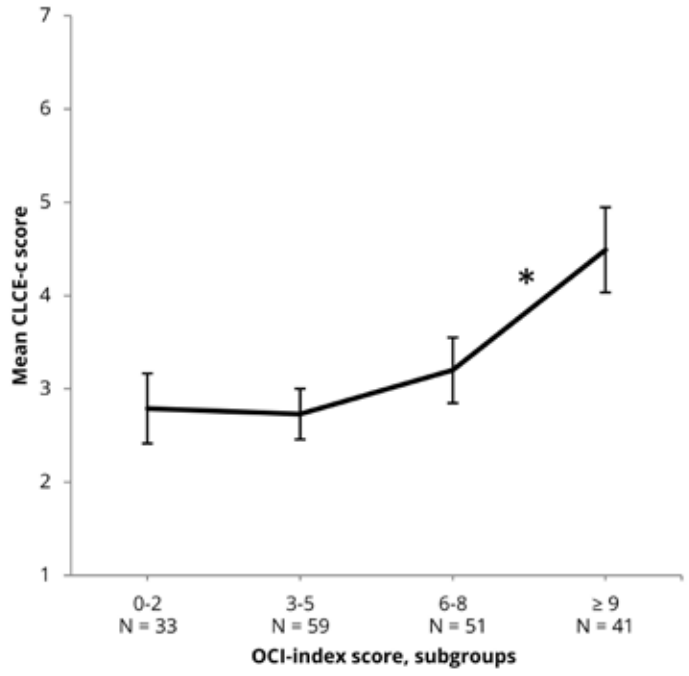
Abbreviations: *MMSE, Mini-Mental State Examination; COWA-FAS, Controlled Oral Word Association Test F-A-S; RBMT, Rivermead Behavioral Memory Test; ROCF, Rey-Osterrieth Complex Figure Test; SD, standard deviation; Stroop, Stroop Color Word Test; VPA, Verbal Paired Associates.*

A total of 187 patients (89.9%) reported at least one SCC-c and 139 patients (66.8%) found at least one SCC to have an impact on daily life (i.e., SCC-w). The mean CLCE-c and CLCE-w scores were 3.4 ± 2.5 and 2.0 ± 2.2, respectively. Prevalence and impact of each of the 13 cognitive SCC items are presented in the Appendix of this chapter, Table A1. Although in bivariate analyses, sex was significantly associated with CLCE scores (CLCE-c: rho = -0.14, p = .05; CLCE-w: rho = -0.15, p = .03; women scored higher than men), and premorbid IQ with CLCE-c (rho = -0.15, p = .04; people with a low IQ had higher scores than those with a high IQ), none of the demographic variables (age, sex, IQ) or clinical variables (stroke severity) was significantly correlated with the CLCE-c and CLCE-w scores (all p-values > .05) in multivariate adjusted analyses.

Association of global objective cognitive performance with subjective cognitive complaints

The OCI-index was significantly correlated with the CLCE-c score in both unadjusted (rho = 0.22, p = .003) and multivariate adjusted (β = 0.25, p = .01) models. The CLCE score increased markedly if the OCI-index was above 8 (i.e., if there were more than 8 neuropsychological (sub)tests scores classified as impaired based on norm-based cut-off values; see Figure 2).

Figure 2. *Mean CLCE-c score as related to objective cognitive impairment index score*



** p < .05 compared with previous level. Error bars represent standard error of the means. Overall effect across the 4 groups (F(3,180) = 4.89, p = .003).* ***Abbreviations:*** *CLCE-c, Checklist for Cognitive and Emotional Consequences following stroke, content; OCI, objective cognitive impairment.*

Associations between OCP and SCC-w showed a similar pattern of results. The OCI-index was significantly correlated with the CLCE-w score (rho = 0.22, p = .003; covariate adjusted β = 0.31, p = .001). Analyses using the CLCE-t score revealed parallel results (rho = 0.23, p = .002; covariate adjusted β = 0.28, p = .002).

Associations of individual neuropsychological tests with subjective cognitive complaints

Table 3 shows the bivariate correlations of separate OCP tests with the CLCE scores. The strongest correlations with CLCE-c score were found for the RBMT total score (rho = -0.30), Stroop cards II and III (rho = 0.25 for both tasks), Category Fluency (rho = -0.25) and Digit Span (rho = -0.24) (all p < .01). Multivariate regression analysis showed that the RBMT was the only neuropsychological test that was independently associated with SCC (β = -0.34, p = .001; see Table 3).

The results for SCC-w were similar and the RBMT was the only test independently associated with CLCE-w in multivariate regression analysis (β = -0.31, p = .002; Appendix, Table A2). Analyses for the CLCE-t score revealed the same pattern of results (Appendix, Table A3).

Item analysis of the association between objective and subjective cognitive measures

Associations between individual neuropsychological (sub)tests and the corresponding individual SCC items were analyzed in five cognitive domains: (i) mental speed and attention, (ii) memory, (iii) executive functioning, (iv) expressive language and (v) visuospatial functioning. Detailed results of these analyses are provided in the Appendix, Tables A4 through A7.

For the CLCE-c items, significant results in multivariate hierarchical logistic regression analyses were found on tests related to the domains of memory, executive functioning and expressive language, but not for the domains of mental speed/attention and visuospatial functioning. Regarding memory, the RBMT was associated with CLCE item 4 (remembering new information) and item 5 (remembering old information). For the executive function domain, the Stroop card III (concept shifting) was associated with SCC related to multi-tasking (CLCE item 1: doing 2 things simultaneously). Item analysis for the expressive language domain showed that Category Fluency was associated with SCC related to verbal abilities (CLCE item 12: speaking or writing).

The item-analysis results for the CLCE-w items were slightly different from those for CLCE-c items (see Tables A4 through A7 in the Appendix). Multivariate logistic regression analyses for the per-item analyses revealed significant OCP – SCC associations in the domains mental speed/attention, memory and executive functioning, but not in expressive language and visuospatial functioning.

DISCUSSION

We found that objectively determined cognitive performance using neuropsychological tests was associated with self-reported cognitive complaints in patients 3 months after stroke. These associations were found at the global level of OCP with a cumulative effect of neuropsychological impairment on subjective complaints. The strongest OCP-SCC associations were observed when ecologically valid tests in the memory domain were used.

Unique to this study is the observation that the number of subjective complaints increased markedly when patients performed poorly (i.e., below the published norm-based cut-off value) on more than 8 neuropsychological tests (Figure 2).

Table 3. *Correlations and multivariate linear regression analyses evaluating the association between objective cognitive performance and subjective cognitive complaints (CLCE-content score).*

Determinant	rho	p-value	Standardized β	p-value
Demographics				
Age	0.12	.09	-0.05	.60
Sex (male)	-0.14	**.05**	-0.12	.12
D-NART	-0.15	**.04**	-0.02	.85
Neuropsychological tasks				
MMSE	-0.17	**.02**	0.05	.59
Stroop I (reading) (time)	0.25	**<.001**	0.09	.60
Stroop II (naming) (time)	0.22	**.001**	Not entered	
Stroop III (interference) (time)	0.25	**<.001**	0.05	.86
Stroop (interference score)	0.08	.25	0.07	.77
Digit-symbol coding	-0.20	**.004**	Not entered	
Digit span	-0.24	**.001**	-0.10	.28
RBMT	-0.30	**<.001**	-0.34	**.001**
ROCF (time needed to copy)	-0.10	.15	-0.04	.61
ROCF (copy score)	-0.12	.08	0.002	.98
ROCF (immediate recall)	-0.11	.11	0.004	.97
ROCF (delayed recall)	-0.11	.13	Not entered	
VPA (immediate recall)	-0.12	.09	Not entered	
VPA (learning slope)	-0.10	.16	Not entered	
VPA (delayed recall)	-0.15	**.04**	0.02	.84
Rule Shift Card	-0.06	.38	0.04	.64
Zoo Map (profile score)	-0.06	.37	0.03	.69
Category fluency	-0.25	**<.001**	-0.14	.19
COWA-F-A-S	-0.13	.07	0.12	.24
Boston Naming Test	-0.10	.14	0.15	.14

Variables that were not entered in the regression analysis were excluded because of strong correlations (Spearman's rho ≥ 0.70) with one or more other tests. ***Abbreviations:*** *COWA-F-A-S, Controlled Oral Word Association Test F-A-S; D-NART, Dutch version of the National Adult Reading Test; IQCODE, Dutch version of the National Adult Reading Test; MMSE, Mini-Mental State Examination; OCP, objective cognitive performance; RBMT, Rivermead Behavioral Memory Test; ROCF, Rey-Osterrieth Complex Figure Test; SCC, subjective cognitive complaints; Stroop, Stroop Color Word Test; VPA, Verbal Paired Associates.*

This finding supports the suggestion by Duits et al. [6] that, although poor cognitive performance on individuals tests do not necessarily result in SCC, in severe cases of poor OCP the SCC may indeed reflect objective cognitive disorders. In other words, the more OCP defects a patient has, the more likely they will report SCC. These findings require replication and further refinement because the OCI-index was based on the number of neuropsychological tests that were used in this project and no weighing for specifically important dimensions or standardized z-score approaches were used. Relying on established norm-based cut-off values may also have influenced the results. In addition, although the correlations between the overall OCI-index and SCC was highly significant and independent of age, sex, and IQ, the effect size of the correlation was of medium magnitude (adjusted regression weight = 0.25 for SCC-c and 0.31 for SCC-w). Future studies are also needed to determine to what extent the effects of objective cognitive dysfunction in multiple domains on SCC translates into more general indices of daily life functioning such as quality of life and activities of daily living (ADL). The present findings indicate that multiple factors other than OCP play a role in patient-reported SCC.

The ecologically valid OCP tests showed the strongest correlations with SCC, particularly in the memory domain. This link between memory-related OCP and SCC has also been observed by Lincoln and Tinson [12] and by Davis et al. [29], who also used the RBMT. Our results may in part be accounted for by the ecological validity of the instruments (e.g., both instruments tapped into the same aspects of memory: remembering a story, a face, or a message in the RBMT were also specifically asked about in the CLCE). This close correspondence between OCP and SCC was less prominent for the other cognitive domains, although we also used an ecologically valid instrument to assess executive functioning (i.e., the BADS). The similarity between the BADS subtests we used (Zoo Map and Rule Shift Cards) and the CLCE questions about SCC in daily life is not as clear-cut as it is for the RBMT. Our results therefore support the suggestion by Lincoln and Tinson [12] and by Mark and Sitskoorn [14] that OCP-SCC links are more likely to be found when OCP measures closely resemble daily life cognitive tasks.

The OCP-SCC association was similar for the two components of SCC (content and worry) when sum scores were analyzed, but differed slightly when associations between specific CLCE items and individual neuropsychological test scores were examined. The majority of the previous studies to date [5, 10, 12, 13, 15, 16, 29] have evaluated SCC-c without exploring the impact of SCC on daily life. The present study indicates that more associations with OCP are found for SCC-w than for SCC-c. These results underscore the importance of making a distinction between the SCC per se and the patient-perceived impact and concerns related to the SCC. Those who experience an impact of their SCC on daily life functioning (compared to those that do not) may be more aware of their objective cognitive limitations and/or may have no adequate strategies to compensate for these

impairments. Duits et al. [6] evaluated the patient perceived impact of SCC, also using the CLCE, and concluded that post-stroke SCC were unrelated to objective cognitive impairment. Based on the present findings, it is possible that the OCP-SCC associations are better assessed when using global indices of cumulative cognitive deficits in addition to individual tests that address specific cognitive domains. Future studies on specific SCC items and parallel ecologically valid neuropsychological tests may shed further light on this clinically important issue.

Several limitations of this study influence the inferences that can be made. The cross-sectional design precludes firm conclusions about causality. In addition, the current literature on post-stroke SCC is complicated by the lack of consensus on the definition of SCC and its critical components. We defined SCC as a construct with two components: the primary index being the content component referring to the number and nature of the patient-reported cognitive difficulties, and the worry component describing to what extent individuals report that their specific content-related SCC have an impact on their daily lives (see also Chapters 2 - 4 [3, 18, 30]). This distinction between the content and worry/impact SCC components requires further validation and replication. We also focused on the cognitive rather than the affect-related aspects of SCC. Furthermore, the present sample of stroke patients consisted mainly of individuals with relatively mild stroke severity (median NIHSS score 3) and a relative good recovery (86% of the patients was recovered well enough to return to their own home environment after discharge). It is possible that the mild severity reflects non-participation of patients with more severe strokes. However, the patients in our sample often scored below established norm-based cut-off values on neuropsychological (Table 2) and, as was shown in Chapter 4 [30], also reported more SCC than a stroke free comparison group. These findings indicate that poor OCP and SCC are both prevalent at 3 months after stroke, even among those with a relative favorable recovery. Also, the current results did not change after including stroke lateralization and stroke severity (NIHSS score) as covariates in the regression analyses (data not shown). Finally, the validity of self-evaluations may be influenced by stroke-related changes in self-awareness, including anosognosia, [31]. We considered using reports of patients' cognitive function by informants, but elect to focus on self-reported cognitive complaints because informant (proxy)-based assessments have interpretational challenges (see for example Wendel et al. [17], Davis et al. [29], Visser-Keizer et al. [32] and Liebermann et al. [33]) and we were specifically interested in the patients' personal experiences of cognitive complaints.

CONCLUSIONS

Poor performance on multiple neuropsychological tests was significantly associated with the presence of SCC measured with the CLCE 3 months after stroke. Cumulative effects of impairments on objective neuropsychological tests and self-reported cognitive complaints were found. In addition, ecologically valid tests in the memory domain were more strongly associated with SCC than traditional neuropsychological tests. These data may suggest that deficits in multiple cognitive domains are important in patients' subjective experiences with cognitive tasks in daily life, as the potential to develop compensatory cognitive strategies may decrease as the number of objective deficits increases. Future research may focus on whether the OCP-SCC associations change when following patients for longer than 3 months after stroke (i.e., early or chronic phase), whether the associations are influenced by psychological factors such as depression and individual coping styles, and to what extent objective and subjective cognitive measures predict quality of life and ADL during long-term follow-up.

REFERENCES

1] de Haan EH, Nys GM, Van Zandvoort MJ. Cognitive function following stroke and vascular cognitive impairment. Curr Opin Neurol. 2006;19:559-564.

2] Cumming TB, Marshall RS, Lazar RM. Stroke, cognitive deficits, and rehabilitation: Still an incomplete picture. Int J Stroke. 2013;8:38-45.

3] van Rijsbergen MW, Mark RE, de Kort PL, Sitskoorn MM. Subjective cognitive complaints after stroke: A systematic review. J Stroke Cerebrovasc Dis. 2014;23:408-420.

4] Pendlebury ST, Mariz J, Bull L, Mehta Z, Rothwell PM. MOCA, ACE-R, and MMSE versus the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery after TIA and Stroke. Stroke. 2012;43:464-469.

5] Lamb F, Anderson J, Saling M, Dewey H. Predictors of subjective cognitive complaint in post-acute older adult stroke patients. Arch Phys Med Rehabil. 2013;94:1747-1752.

6] Duits A, Munnecom T, van Heugten C, van Oostenbrugge RJ. Cognitive complaints in the early phase after stroke are not indicative of cognitive impairment. J Neurol Neurosurg Psychiatry. 2008;79:143-146.

7] Maaijwee NA, Schaapsmeerders P, Rutten-Jacobs LC, Arntz RM, Schoonderwaldt HC, van Dijk EJ, et al. Subjective cognitive failures after stroke in young adults: Prevalent but not related to cognitive impairment. J Neurol. 2014;261:1300-1308.

8] Narasimhalu K, Wiryasaputra L, Sitoh YY, Kandiah N. Post-stroke subjective cognitive impairment is associated with acute lacunar infarcts in the basal ganglia. Eur J Neurol. 2013;20:547-551.

9] Van Heugten C, Rasquin S, Winkens I, Beusmans G, Verhey F. Checklist for cognitive and emotional consequences following stroke (CLCE-24): Development, usability and quality of the self-report version. Clin Neurol Neurosurg. 2007;109:257-262.

10] Xiong YY, Wong A, Mok VC, Tang WK, Lam WW, Kwok TC, et al. Frequency and predictors of proxy-confirmed post-stroke cognitive complaints in lacunar stroke patients without major depression. Int J Geriatr Psychiatry. 2011;26:1144–1151.

11] Winkens I, Van Heugten CM, Fasotti L, Wade DT. Reliability and validity of two new instruments for measuring aspects of mental slowness in the daily lives of stroke patients. Neuropsychol Rehabil. 2009;19:64-85.

12] Lincoln NB, Tinson DJ. The relation between subjective and objective memory impairment after stroke. Br J Clin Psychol. 1989;28 (Pt 1):61-65.

13] Aben L, Ponds RW, Heijenbrok-Kal MH, Visser MM, Busschbach JJ, Ribbers GM. Memory complaints in chronic stroke patients are predicted by memory self-efficacy rather than memory capacity. Cerebrovasc Dis. 2011;31:566-572.

14] Mark RE, Sitskoorn MM. Are subjective cognitive complaints relevant in preclinical alzheimer's dementia? A review and guidelines for healthcare professionals. Rev Clin Gerontol. 2013;23 61-74.

15] Narasimhalu K, Wiryasaputra L, Sitoh YY, Kandiah N. Post-stroke subjective cognitive impairment is associated with acute lacunar infarcts in the basal ganglia. Eur J Neurol. 2013;20:547-551.

16] van Heugten C, Rasquin S, Winkens I, Beusmans G, Verhey F. Checklist for cognitive and emotional consequences following stroke (CLCE-24): Development, usability and quality of the self-report version. Clin Neurol Neurosurg. 2007;109:257-262.

17] Wendel K, Risberg J, Pessah-Rasmussen H, Stahl A, Iwarsson S. Long-term cognitive functional limitations post stroke: Objective assessment compared with self-evaluations and spouse reports. Int J Rehabil Res. 2008;31:231-239.

18] van Rijsbergen MW, Mark RE, de Kort PL, Sitskoorn MM. The COMPlaints After Stroke (COMPAS) study: Protocol for a Dutch cohort study on poststroke subjective cognitive complaints. BMJ Open. 2013;3:e003599.

19] Brott T, Adams HP, Jr., Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: A clinical examination scale. Stroke. 1989;20:864-870.

20] de Jonghe JF, Schmand B, Ooms ME, Ribbe MW. [Abbreviated form of the informant questionnaire on cognitive decline in the elderly]. Tijdschr Gerontol Geriatr. 1997;28:224-229.

21] Spreen O, Strauss E. A compendium of neuropsychological tests administration, norms and commentary. 2nd Ed. New York: Oxford University Press; 1998.

22] Lezak MD, Howieson DB, Loring DW. Neuropsychological Assessment. 4th Ed. New York, NY: Oxford University Press; 2004.

23] Davis JJ, Axelrod BN, McHugh TS, Hanks RA, Millis SR. Number of impaired scores as a performance validity indicator. J Clin Exp Neuropsychol. 2013;35:413-420.

24] Silk-Eglit GM, Miele AS, Stenclik JH, Lynch JK, McCaffrey RJ. Evaluation of the generalizability of the number of abnormal scores and the overall test battery mean as measures of performance validity to a different test battery. Appl Neuropsychol Adult. 2015;22:399-406.

25] Nijsse B, van Heugten CM, van Mierlo ML, Post MW, de Kort PL, Visser-Meily JM. Psychological factors are associated with subjective cognitive complaints 2 months post-stroke. Neuropsychol Rehabil. 2017;27:99-115.

26] van Rijsbergen MW, Mark RE, de Kort PL, Sitskoorn MM. Prevalence and profile of poststroke subjective cognitive complaints. J Stroke Cerebrovasc Dis. 2015;24:1823-1831

27] Schmand B, Bakker D, Saan R, Louman J. [The Dutch adult reading test: A measure of premorbid intelligence]. Tijdschr Gerontol Geriatr. 1991;22:15-19.

28] Blake H, McKinney M, Treece K, Lee E, Lincoln NB. An evaluation of screening measures for cognitive impairment after stroke. Age Ageing. 2002;31:451-456.

29] Davis AM, Cockburn JM, Wade DT, Smith PT. A subjective memory assessment questionnaire for use with elderly people after stroke. Clin Rehabil. 1995;9:238-244.

30] van Rijsbergen MW, Mark RE, de Kort PL, Sitskoorn MM. Prevalence and profile of poststroke subjective cognitive complaints. J Stroke Cerebrovasc Dis. 2015;24:1823-1831.

31] Nurmi Laihosalo ME, Jehkonen M. Assessing anosognosias after stroke: A review of the methods used and developed over the past 35 years. Cortex. 2014;61:43-63.

32] Visser-Keizer AC, Meyboom-de Jong B, Deelman BG, Berg IJ, Gerritsen MJ. Subjective changes in emotion, cognition and behaviour after stroke: Factors affecting the perception of patients and partners. J Clin Exp Neuropsychol. 2002;24:1032-1045.

33] Liebermann D, Ostendorf F, Kopp UA, Kraft A, Bohner G, Nabavi DG, et al. Subjective cognitive-affective status following thalamic stroke. J Neurol. 2013;260:386-396.

CHAPTER 5
APPENDIX

Table A1. *Prevalence of subjective cognitive complaints based on the CLCE*

	Absent	Uncertain	Present	
			No impact	Impact
1. Doing 2 things at once	137 (65.9)	1 (0.5)	31 (14.9)	39 (18.8)
2. Attending to things	129 (62.0)	1 (0.5)	21 (10.1)	57 (27.4)
3. Have become slower	147 (70.7)	1 (0.5)	25 (12.0)	35 (16.8)
4. Remembering new information	111 (53.4)	0	43 (20.7)	54 (26.0)
5. Remembering old information	117 (56.3)	0	40 (19.2)	51 (24.5)
6. Taking initiative	127 (61.1)	3 (1.4)	29 (13.9)	49 (23.6)
7. Planning and organising	174 (83.7)	1 (0.5)	10 (4.8)	23 (11.1)
8. Performing daily activities	204 (98.1)	0	1 (0.5)	3 (1.4)
9. Perceiving time	179 (86.1)	1 (0.5)	19 (9.1)	9 (4.3)
10. Orienting to places or persons	201 (96.6)	1 (0.5)	1 (0.5)	5 (2.4)
11. Understanding language	181 (87.0)	3 (1.4)	5 (2.4)	19 (9.1)
12. Speaking or writing	101 (48.6)	2 (1.0)	41 (19.7)	64 (30.8)
13. Attending to a part of the body or space	199 (95.7)	1 (0.5)	1 (0.5)	7 (3.4)

Numbers are number of respondents (%). ***Abbreviations:*** *CLCE, Checklist for Cognitive and Emotional Consequences following stroke; SCC, subjective cognitive complaints.*

Table A2. *Correlations and multivariate linear regression analyses evaluating the association between post-stroke objective cognitive performance and subjective cognitive complaints (CLCE-w)*

Determinant	rho	p-value	Standardized β	p-value
Demographics				
Age	0.02	.81	-0.14	.15
Sex (male)	-0.15	**.03**	-0.10	.21
D-NART	-0.11	.13	0.03	.76
Neuropsychological tasks				
MMSE	-0.16	**.02**	0.04	.71
Stroop I (reading) (time)	0.26	**<.001**	0.04	.82
Stroop II (naming) (time)	0.22	**.002**	Not entered	
Stroop III (interference) (time)	0.17	**.02**	0.28	.30
Stroop (interference score)	-0.004	.96	-0.20	.37
Digit-symbol coding	-0.16	**.02**	0.07	.61
Digit span	-0.22	**.002**	-0.11	.24
RBMT	-0.19	**.01**	-0.31	**.002**
ROCF (time needed to copy)	0.07	.30	-0.04	.65
ROCF (copy score)	-0.08	.25	0.03	.73
ROCF (immediate recall)	-0.03	.63	-0.002	.98
ROCF (delayed recall)	-0.02	.73	Not entered	
VPA (immediate recall)	-0.08	.28	0.001	.99
VPA (learning slope)	-0.10	.19	Not entered	
VPA (delayed recall)	-0.08	.29	Not entered	
Rule Shift Card	0.01	.87	0.07	.41
Zoo Map (profile score)	0.05	.45	0.11	.17
Category fluency	-0.16	**.02**	-0.03	.80
COWA-F-A-S	-0.10	.14	0.03	.80
Boston Naming Test	-0.13	.06	-0.07	.47

Variables that were not entered in the regression analysis were excluded because of strong correlations (Spearman's rho ≥ 0.70) with one or more other tests. ***Abbreviations:*** *COWA-F-A-S, Controlled Oral Word Association Test F-A-S; D-NART, Dutch version of the National Adult Reading Test; IQCODE, Dutch version of the National Adult Reading Test; MMSE, Mini-Mental State Examination; OCP, objective cognitive performance; RBMT, Rivermead Behavioral Memory Test; ROCF, Rey-Osterrieth Complex Figure Test; SCC, subjective cognitive complaints; Stroop, Stroop Color Word Test; VPA, Verbal Paired Associates.*

Table A3. *Correlations and multivariate linear regression analyses evaluating the association between post-stroke objective cognitive performance and subjective cognitive complaints (CLCE-t)*

Determinant	rho	p-value	Standardized β	p-value
Demographics				
Age	0.10	.15	-0.07	.43
Sex (male)	-0.15	**.03**	-0.11	.17
D-NART	-0.14	**.04**	0.004	.97
Neuropsychological tasks				
MMSE	-0.17	**.01**	0.05	.62
Stroop I (reading) (time)	0.26	**<.001**	0.15	.13
Stroop II (naming) (time)	0.23	**.001**	Not entered	
Stroop III (interference) (time)	0.24	**.001**	Not entered	
Stroop (interference score)	0.07	.35	0.08	.35
Digit-symbol coding	-0.20	**.004**	0.07	.58
Digit span	-0.24	**<.001**	-0.12	.21
RBMT	-0.28	**<.001**	-0.35	**<.001**
ROCF (time needed to copy)	0.10	.15	-0.03	.73
ROCF (copy score)	-0.12	.09	0.003	.98
ROCF (immediate recall)	-0.10	.17	0.002	.99
ROCF (delayed recall)	-0.09	.21	Not entered	
VPA (immediate recall)	-0.12	.10	0.03	.78
VPA (learning slope)	-0.11	.13	Not entered	
VPA (delayed recall)	-0.14	.05	Not entered	
Rule Shift Card	-0.05	.48	0.06	.54
Zoo Map (profile score)	-0.03	.64	0.06	.47
Category fluency	-0.24	**.001**	-0.13	.25
COWA-F-A-S	-0.13	.06	0.08	.39
Boston Naming Test	-0.12	.08	0.07	.46

Variables that were not entered in the regression analysis were excluded because of strong correlations (Spearman's rho ≥ 0.70) with one or more other tests. ***Abbreviations:*** *COWA-F-A-S, Controlled Oral Word Association Test F-A-S; D-NART, Dutch version of the National Adult Reading Test; IQCODE, Dutch version of the National Adult Reading Test; MMSE, Mini-Mental State Examination; OCP, objective cognitive performance; RBMT, Rivermead Behavioral Memory Test; ROCF, Rey-Osterrieth Complex Figure Test; SCC, subjective cognitive complaints; Stroop, Stroop Color Word Test; VPA, Verbal Paired Associates.*

Table A4. *Item-specific analysis for the association between post-stroke objective cognitive performance and subjective cognitive complaints: mental speed and attention*

		CLCE-c			CLCE-w		
		Correlations		Logistic Regression Analysis	Correlations		Logistic regression Analysis
CLCE item	Determinants	rho	p-value	Odds Ratio (95% CI)	rho	p-value	Odds Ratio (95% CI)
2. Attending to things	Age	-0.12	.08	0.98 (0.95 – 1.01)	-0.11	.11	0.97 (0.94 – 1.00)
	Sex (male)	-0.001	.99	0.99 (0.53 – 1.87)	-0.04	.62	0.86 (0.432 – 1.73)
	IQ (D-NART)	0.11	.11	1.02 (0.99 – 1.05)	0.04	.55	1.02 (0.99 – 1.06)
	Stroop I (reading)	0.01	.92	Not entered	0.11	.11	**1.04 (1.01 – 1.07)**
	Stroop II (naming)	0.04	.60	1.02 (0.99 – 1.04)	0.08	.23	Not entered
	Digit-symbol coding	0.03	.65	1.00 (0.98 – 1.03)	-0.02	.82	1.00 (0.97 – 1.03)
3. Have become slower	Age	0.24	**.001**	1.03 (0.99 – 1.06)	0.17	**.02**	1.02 (0.98 – 1.06)
	Sex (male)	-0.16	**.02**	0.61 (0.30 – 1.22)	-0.19	**.01**	**0.41 (0.18 – 0.94)**
	IQ (D-NART)	-0.26	**<.001**	**0.96 (0.93 – 0.99)**	-0.21	**.003**	**0.96 (0.93 – 0.99)**
	Stroop I (reading)	0.23	**.001**	Not entered	0.16	**.02**	1.02 (0.99 – 1.05)
	Stroop II (naming)	0.23	**.001**	1.00 (0.98 – 1.03)	0.15	**.02**	Not entered
	Digit-symbol coding	-0.25	**<.001**	0.99 (0.97 – 1.03)	-0.19	**.01**	1.00 (0.97 – 1.04)

Stroop I was not entered in the regression analysis because of a strong correlations (Spearman's rho=0.81) with Stroop II (both for SCC-content and SCC-worry). ***Abbreviations:*** *CLCE, Checklist for Cognitive and Emotional Consequences following stroke, content, worry score; OCP, objective cognitive performance; SCC, subjective cognitive complaints; Stroop, Stroop Color Word Test*

Table A5. *Item-specific analysis for the association between post-stroke objective cognitive performance and subjective cognitive complaints: memory*

		CLCE-c			CLCE-w		
		Correlations		Logistic Regression Analysis	Correlations		Logistic Regression Analysis
CLCE item	Determinants	rho	p-value	Odds Ratio (95% CI)	rho	p-value	Odds Ratio (95% CI)
4. Remembering new information	Age	0.12	.08	1.00 (0.98 – 1.03)	0.04	.61	0.99 (0.96 – 1.02)
	Sex (male)	-0.10	.15	0.66 (0.34 – 1.31)	-0.06	.39	0.77 (0.37 – 1.63)
	IQ (D-NART)	-0.12	.09	1.01 (0.98 – 1.04)	-0.15	**.04**	1.09 (0.97 – 1.05)
	RBMT	-0.26	**<.001**	**0.87 (0.79 – 0.96)**	-0.15	**.04**	0.91 (0.82 – 1.00)
	ROCF– immediate recall	-0.13	.06	1.01 (0.96 – 1.06)	-0.12	.09	1.00 (0.95 – 1.06)
	VPA immediate recall	-0.13	.07	0.99 (0.94 – 1.04)	-0.17	**.02**	Not entered
	VPA learning slope	-0.11	.12	Not entered	-0.18	**.01**	0.90 (0.74 – 1.10)
	Digit span	-0.18	**.01**	0.95 (0.85 – 1.06)	-0.24	**<.001**	**0.87 (0.76 – 0.99)**
5. Remembering old information	Age	0.12	.08	0.99 (0.97 – 1.02)	0.04	.55	0.98 (0.95 – 1.01)
	Sex (male)	-0.12	.08	0.51 (0.26 – 1.01)	-0.09	.22	0.55 (0.26 – 1.18)
	IQ (D-NART)	-0.15	**.03**	1.02 (0.98 – 1.05)	-0.09	.19	1.02 (0.98 – 1.06)
	RBMT	-0.26	**<.001**	**0.87 (0.78 – 0.96)**	-0.18	**.01**	**0.87 (0.78 – 0.97)**
	ROCF– delayed recall	-0.15	**.04**	1.02 (0.97 – 1.07)	-0.12	.10	1.01 (0.95 – 1.07)
	VPA delayed recall	-0.19	**.01**	0.92 (0.80 – 1.08)	-0.14	.06	0.90 (0.75 – 1.07)
	Digit span	-0.27	**<.001**	0.89 (0.79 – 1.00)	-0.16	**.02**	0.93 (0.82 – 1.06)

VPA learning slope= 0.74 with CLCE-content and rho = 0.75 with CLCE-worry). ***Abbreviations:*** *CLCE, Checklist for Cognitive and Emotional Consequences following stroke, content, worry score; OCP, objective cognitive performance; RBMT, Rivermead Behavioral Memory Test; ROCF, Rey-Osterrieth Complex Figure Test; SCC, subjective cognitive complaints; VPA, Verbal Paired Associates.*

Table A6. *Item-specific analysis for the association between post-stroke objective cognitive performance and subjective cognitive complaints: executive functioning*

		CLCE-c			CLCE-w		
		Correlations		Logistic Regression Analysis	Correlations		Logistic Regression Analysis
CLCE item	Determinants	rho	p-value	Odds Ratio (95% CI)	rho	p-value	Odds Ratio (95% CI)
1. Doing 2 things at once	Age	0.02	.82	0.99 (0.96 – 1.02)	-0.07	.32	0.98 (0.94 – 1.01)
	Sex (male)	-0.08	.25	0.64 (0.33 – 1.23)	-0.07	.32	0.62 (0.28 – 1.35)
	IQ (D-NART)	-0.08	.23	1.00 (0.97 – 1.03)	-0.02	.81	1.01 (0.98 – 1.05)
	Stroop III, time	0.22	**.002**	**1.02 (1.01 – 1.03)**	0.15	**.03**	**1.02 (1.01 – 1.03)**
	Stroop, interference score	0.10	.16	0.65 (0.23 – 1.84)	0.04	.54	0.38 (0.12 – 1.23)
	Rule Shift Cards	0.02	.75	1.26 (0.89 – 1.78)	0.03	.71	1.10 (0.73 – 1.67)
	Zoo Map	0.08	.27	1.20 (0.91 – 1.60)	0.12	.08	1.31 (0.93 – 1.83)
6. Taking initiative	Age	-0.004	.95	1.01 (0.98 – 1.03)	-0.11	.21	0.98 (0.95 – 1.01)
	Sex (male)	0.03	.62	1.14 (0.60 – 2.14)	-0.03	.66	0.70 (0.34 – 1.47)
	IQ (D-NART)	0.05	.51	1.01 (0.98 – 1.03)	0.02	.78	1.00 (0.97 – 1.04)
	Stroop III, time	-0.07	.30	1.00 (0.99 – 1.02)	-0.09	.21	1.01 (0.99 – 1.02)
	Stroop, interference score	-0.11	.13	0.53 (0.20 – 1.39)	-0.16	**.02**	**0.22 (0.06 – 0.80)**
	Rule Shift Cards	0.02	.78	1.01 (0.73 – 1.38)	-0.01	.92	0.81 (0.55 – 1.19)
	Zoo Map	0.09	.21	1.15 (0.88 – 1.49)	-0.16	**.02**	**1.40 (1.02 - 1.93)**
7. Planning and organizing	Age	-0.08	.26	0.98 (0.94 – 1.02)	-0.15	**.03**	0.96 (0.92 – 1.01)
	Sex (male)	-0.07	.35	0.73 (0.32 – 1.70)	-0.01	.95	0.80 (0.29 – 2.21)
	IQ (D-NART)	0.02	.78	1.01 (0.97 – 1.05)	0.07	.35	1.02 (0.97 – 1.07)
	Stroop III, time	-0.01	.56	1.01 (0.99 – 1.02)	-0.06	.41	1.01 (0.99 – 1.03)
	Stroop, interference score	-0.06	.41	0.49 (0.12 – 1.93)	-0.08	.27	0.32 (0.06 – 1.80)
	Rule Shift Cards	0.01	.87	0.79 (0.51 – 1.22)	0.05	.45	0.91 (0.51 – 1.60)
	Zoo Map, total score	0.09	.22	1.28 (0.89 – 1.85)	0.15	**.04**	1.47 (0.94 – 2.31)

Table A6 *Continued*

		CLCE-c			CLCE-w		
		Correlations		Logistic Regression Analysis	Correlations		Logistic Regression Analysis
CLCE item	Determinants	rho	p-value	Odds Ratio (95% CI)	rho	p-value	Odds Ratio (95% CI)
8. Performing daily activities	Age	-0.06	.39	NA	-0.02	.82	NA
	Sex (male)	0.03	.71	NA	0.002	.98	NA
	IQ (D-NART)	-0.02	.75	NA	0.002	.98	NA
	Stroop III, time	-0.001	.99	NA	-0.04	.60	NA
	Stroop, interference score	-0.05	.46	NA	-0.04	.55	NA
	Rule Shift Cards	0.07	.31	NA	0.04	.58	NA
	Zoo Map, total score	0.09	.23	NA	0.03	.71	NA

Abbreviations: *CLCE, Checklist for Cognitive and Emotional Consequences following stroke, content, worry score; NA, Not applicable, sample size is too small; COWA-F-A-S, Controlled Oral Word Association Test F-A-S; OCP, objective cognitive performance; SCC, subjective cognitive complaints; Stroop, Stroop Color Word Test.*

Table A7. *Item-specific analysis for the association between post-stroke objective cognitive performance and subjective cognitive complaints: expressive language and visuospatial functioning*

		CLCE-c			CLCE-w		
		Correlations		Logistic regression Analysis	Correlations		Logistic Regression Analysis
CLCE item	Determinants	rho	p-value	Odds Ratio (95% CI)	rho	p-value	Odds Ratio (95% CI)
12. Speaking or writing	Age	0.15	**.04**	1.01 (0.98 – 1.04)	0.13	.07	1.01 (0.98 – 1.04)
	Sex (male)	-0.09	.19	0.72 (0.39 – 1.35)	-0.09	.19	0.80 (0.41 – 1.58)
	IQ (D-NART)	-0.18	**.01**	0.99 (0.96 – 1.02)	-0.20	**.004**	0.99 (0.96 – 1.03)
	Boston Naming Test	-0.11	.11	1.03 (1.00 – 1.06)	-0.22	**.002**	1.00 (0.97 – 1.03)
	Category fluency	-0.30	**<.001**	**0.94 (0.90 – 0.99)**	-0.29	**<.001**	0.98 (0.94 – 1.03)
	COWA-F-A-S	-0.22	**.002**	1.00 (0.96 – 1.04)	-0.26	**<.001**	0.96 (0.91 – 1.00)
13. Attending to a part of the body or space	Age	0.15	**.04**	1.00 (0.94 – 1.07)	0.003	.96	0.99 (0.92 – 1.06)
	Sex (male)	-0.15	**.04**	0.32 (0.07 – 1.49)	-0.09	.19	0.55 (0.10 – 3.00)
	IQ (D-NART)	0.04	.58	1.00 (0.95 – 1.07)	0.04	.60	0.99 (0.92 – 1.06)
	ROCF – copy time	0.15	**.03**	0.95 (0.85 – 1.05)	0.11	.11	0.99 (0.86 – 1.13)
	ROCF – copy score	-0.10	.17	1.00 (1.00 – 1.01)	-0.08	.28	1.00 (0.99 – 1.01)

Abbreviations: *CLCE, Checklist for Cognitive and Emotional Consequences following stroke, content, worry score; COWA-F-A-S, Controlled Oral Word Association Test F-A-S; OCP, objective cognitive performance; ROCF, Rey-Osterrieth Complex Figure Test; SCC, subjective cognitive complaints*

CHAPTER 6

PSYCHOLOGICAL FACTORS AND SUBJECTIVE COGNITIVE COMPLAINTS AFTER STROKE:
BEYOND DEPRESSION AND ANXIETY

BASED ON:
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ABSTRACT

Objective: Subjective cognitive complaints (SCC) are common after stroke and are related to objective cognitive impairment, although this is not a consistent finding. We determined whether depression, anxiety, perceived stress and fatigue are associated with post-stroke SCC and whether these associations are independent of objective cognitive functioning, stroke characteristics and individual differences in personality traits and coping styles.

Methods: Using a cross-sectional design, SCC and psychological measures were obtained in 208 patients (mean age 64.9 ± 12.4 years; 65.9% men) 3 months after stroke (mean 3.3 ± 0.5 months). SCC were assessed using the Checklist for Cognitive and Emotional consequences following stroke (CLCE) inventory. Validated questionnaires were used to measure depression and anxiety (HADS), perceived stress (PSS-4), fatigue (FAS), personality traits (EPQ-RSS) and coping style (UCL). Multivariate hierarchical linear regression analyses were used to adjust for covariates.

Results: Depression (standardized β = 0.35), anxiety (standardized β = 0.38), perceived stress (standardized β = 0.39) and fatigue (standardized β = 0.39) were associated with CLCE scores, independent of demographic, stroke-related and cognitive performance covariates. After including personality traits and coping styles into the model, independent associations with CLCE scores were obtained for fatigue (standardized β = 0.26, p = .003) and neuroticism (standardized β = 0.21, p = .05).

Conclusions: Depression, anxiety, perceived stress and fatigue were associated with SCC 3 months after stroke. Neuroticism may be a common factor accounting for these associations, with the exception of fatigue, which remained independently associated with SCC. Interventions aimed at increasing energy levels and psychological resilience might prove a worthwhile addition to stroke rehabilitation programs by reducing SCC and improving quality of life.

INTRODUCTION

Subjective cognitive complaints (SCC) are common after stroke, with prevalence estimates ranging between 28.6% [1] and 92.0% [2]. These complaints occur early after stroke and often remain present until years after the event [3-7]. The most commonly reported SCC in this population include mental slowness, concentration difficulties and memory problems (see Chapter 2 [8]). The biomedical and psychological factors that play a role in post-stroke SCC are not well understood. Evidence suggests that objective indices of cognitive performance based on neuropsychological testing show correlations with post-stroke SCC as well as functioning after stroke as assessed using measures of activities of daily living (ADL) [9-13]. However, the reported associations are relatively weak, and these factors do not explain the high prevalence of SCC in post-stroke patients (see Chapter 2 [8], Chapter 4 [14] and 5 [15]).

Multiple studies indicate that psychological factors are related to SCC, particularly post-stroke depression [2, 4, 5, 12, 13, 16-18]. Most studies demonstrated that post-stroke depressive symptoms are associated with more SCC [2, 4, 5, 12, 13, 16-18], although one study did not find such a relationship [10]. Other psychosocial aspects known to occur frequently after stroke (e.g., anxiety and fatigue) have also been examined. Two studies reported that post-stroke anxiety was associated with SCC, but these associations were attenuated in multivariate adjusted models [5, 17]. The relationship between post-stroke fatigue and SCC have also revealed mixed results (two studies found an association [12, 17] and one did not [2]). Symptoms of depression, anxiety and fatigue are interrelated after stroke and are an indication of psychological distress [19]. Which of these aspects is the most important in relation to SCC is yet unknown. It is also possible that depression, anxiety and fatigue reflect a general factor of psychological distress that is associated with SCC in post-stroke patients.

Studies on SCC in the general population have shown that personality traits, neuroticism in particular, are strongly associated with SCC [20, 21]. Whether this is also true for patients who had a stroke, is less well established. Aben et al. [16] found a relationship between neuroticism and memory-related SCC, which became non-significant in covariate-adjusted models. An association with extraversion or coping style with post-stroke SCC was not found in that study [16]. Nijsse et al. [5] reported an independent association between coping style (proactive coping) with the total number of SCC after stroke, whereas no relationships between neuroticism or extraversion with SCC were found. As personality traits and coping styles are known to be associated with measures of psychological distress, such as anxiety and depressive symptoms (see for example Aben et al. [22]), these factors may play an additional role in post-stroke SCC.

The inconsistent results in the literature on the links between psychological variables and SCC may partly be explained by the differences in stroke samples evaluated (e.g., primary focus on patients discharged home [4, 11, 16, 18], or patients

with a minor stroke [10, 13]), variability in the time interval after stroke used to assess SCC (e.g., early [4, 10, 13] or chronic phase [16, 17]) and how SCC was defined and measured (see Chapter 2 [8]). We defined SCC as a psychological construct with two components, a primary *content* component (SCC-content; SCC-c) referring to the nature of cognitive difficulties, and an impact or *worry* component (SCC-worry, SCC-w) describing whether individuals report that their specific content-related SCC have an impact on their daily lives (see also Chapters 2 – 5 [8, 14, 15, 23]).

In the present study, we examined: (1) to what extent distress-related psychological factors that are common in post-stroke patients (depression, anxiety, perceived stress, and fatigue) are related to SCC at 3 months after stroke, and (2) whether the association between these distress-related psychological measures with SCC changes after taking demographic characteristics, stroke severity, objective cognitive performance, ADL, personality traits and coping style into account. We also explored whether the psychological variables related to SCC-w differ from those related to SCC-c.

METHODS

Design and procedure

The current cross-sectional study reports data from the 3 months post-stroke assessment of the COMPlaints After Stroke (COMPAS) study (see Chapter 3 [23]). Between October 2009 and August 2012, patients were recruited from the Elisabeth-TweeSteden Hospital and the Maxima Medical Center, The Netherlands. The medical ethics committees of these hospitals approved the protocol and written informed consent was obtained from all individuals participating in this study.

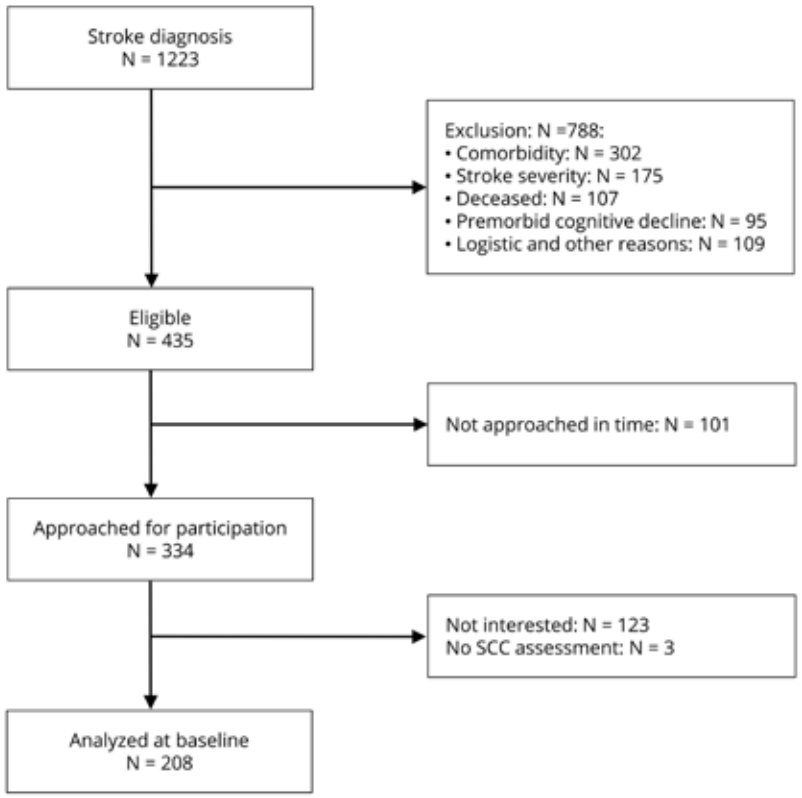
Three months after stroke (mean 3.3 ± 0.5 months), participants were invited to one of the hospitals for the assessment of SCC and neuropsychological test performance on multiple cognitive domains. Psychological questionnaires were completed at home and returned by mail. A reminder was sent when questionnaires were not returned within 2 weeks.

Participants

Patients with a clinical diagnosis of stroke (either ischemic or hemorrhagic, first-ever or recurrent) and aged ≥ 18 years were eligible for this study. Exclusion criteria were: premorbid health problems interfering with cognitive functioning (e.g., cognitive decline, as defined by a score > 3.6 on the short version of the Informant Questionnaire on Cognitive Decline in the Elderly [24]), life-threatening progressive diseases (e.g., cancer or kidney failure), a recent history of psychopathology, and/or severe communication difficulties.

Four hundred and thirty-five patients were eligible, of whom 208 (47.8%) agreed to participate and had an SCC assessment (see Figure 1). Non-participants (i.e. patients who refused inclusion, N = 123), or could not be approached in time for the assessment (N = 101), and those who had no SCC assessment (N = 3), did not differ from participants regarding stroke type (93.0% versus 94.7% had an ischemic stroke, $\chi^2(1) = 0.58$, p = .45), but they more often had a left-sided lesion (56.5% versus 42.9%, $\chi^2(1) = 7.1$, p = .01) and were less severely affected by their stroke at time of admission (National Institutes of Health Stroke Scale, NIHSS [25], median score = 2, interquartile range (IQR) = 1 - 4 versus median score = 3, IQR = 2 - 5; U = 18088.5, p = .03). Non-participants were also older (69.6 ± 12.4 versus 64.9 ± 12.4 years, t(433) = -4.1, p < .001) and were more often female (44.5% versus 34.1%, $\chi^2(1) = 4.9$, p = .03).

Figure 1. *Flow-chart of the study population*



Abbreviation: *SCC, subjective cognitive complaints*

Materials

Subjective cognitive complaints

Assessments of SCC were obtained using the Checklist for Cognitive and Emotional consequences following stroke (CLCE) [11] inventory. The CLCE is a semi-structured interview exploring post-stroke cognitive, emotional and behavioral complaints. Thirteen of the 24 items focus on self-reported cognitive problems and were used in the present study. Each item was scored on presence and interference in daily

life: 0 (SCC not present), 1 (presence uncertain), 2 (present, but not affecting daily life), 3 (present and negatively affecting daily life). The CLCE-content (CLCE-c) score, defined as the number of SCC present irrespective of whether these interfered with daily life, was calculated by dichotomizing each item score into 'absent' (original item score 0) and 'present' (item score 1 through 3) and summing the items (range CLCE-c score = 0-13). In addition, the CLCE-worry (CLCE-w) score, defined as the number of SCC having an impact on daily life, was calculated by dichotomizing each item into 'absence of interference' (item score 0 through 2) or 'presence of interference' (item score 3) and summed over the 13 items (range CLCE-w score = 0-13). This procedure for analyzing the CLCE has been used before [4, 5]. We furthermore calculated the CLCE-total cognitive (CLCE-t) score by summing the original item scores (range 0-39). The CLCE has previously been validated in stroke patients [11]. The internal consistency was found to be good (Cronbach's α = 0.81 based on 22 items) [11]. In the present study Cronbach's α was 0.71 for CLCE-c, 0.75 for CLCE-w, and 0.74 for total CLCE-t score.

Depressive symptoms and anxiety

The Hospital Anxiety and Depression Scale (HADS) [26] was used to assess current self-reported symptoms of depression (7 items, HADS-D) and anxiety (7 items, HADS-A). The total score for both subscales ranges between 0 and 21, with higher scores indicating more symptoms of depression or anxiety. The HADS has demonstrated good psychometric properties as a screening instrument both after stroke and in several other populations with Cronbach's α above 0.80 [27, 28].

Perceived Stress

The Perceived Stress Scale-short form (PSS-4) [29] explores the degree to which recent situations in life are perceived as stressful. The items are answered on a 5-point scale ranging from 0 (never) to 4 (very often). The total score ranges between 0 and 16, with a higher score indicating more perceived stress. The psychometric properties of the PSS-4 were found to be satisfactory in previous studies [30].

Fatigue

The Fatigue Assessment Scale (FAS) [31] (10 items) focuses on self-reported symptoms of fatigue. The items are rated on a 5-point scale ranging from 1 (never) to 5 (always). The total score ranges between 10 and 50, with higher scores indicating more fatigue. The FAS is a useful measure of post-stroke fatigue because of its adequate face validity, feasibility, high test-retest reliability and high construct validity [32]. The internal consistency of the FAS is usually relatively low because the instrument measures different aspects of fatigue (i.e., mental and physical fatigue) [32].

Personality traits

Neuroticism and extraversion were assessed using the two corresponding subscales of the Eysenck Personality Questionnaire Revised Short Scale (EPQ-RSS) [33]. Each scale consists of 12 dichotomized items (yes/no), with a total score ranging from 0 to 12. A higher score indicates more characteristics of the specific personality trait. The EPQ-RSS has demonstrated good internal consistency, test-retest reliability and concurrent validity [34].

Coping style

The abbreviated version of the Utrecht Coping List (UCL) [35-37] contains 15 items from which four styles are distinguished, including: active, social support seeking, avoiding, and palliative coping. Each item is rated on a 4-point rating scale ranging from 1 (never) to 4 (very often). Total scores are computed for each domain with higher scores indicating a greater tendency to adopt the particular coping style. The UCL has moderate to good internal consistency and test-retest reliability [36].

Covariates

Demographics and stroke-related measures were obtained from the patients' medical records. Stroke characteristics (type, side and stroke severity, assessed by the National Institutes of Health Stroke Scale, NIHSS [25]) and discharge destination were recorded by the treating neurologists during hospitalization for stroke. Standardized neuropsychological testing was used to determine objective cognitive performance and to calculate the objective cognitive impairment (OCI) index score (i.e., total number of impaired (sub)test scores, range 0-20); a procedure previously described by Davis et al. [38] and modified for purposes of this study (see Chapter 5 [15]). The rationale for using this composite index is to reduce the number of covariates in the statistical models and because this index showed to be significantly associatedwith SCC (Chapter 5 [15]). Self-report data were used to estimate the pre-stroke intelligence quotient (IQ, using the National Adult Reading Test, D-NART [39]) and instrumental ADL was assessed using the Frenchay Activities Index (FAI) [40].

Statistical Analysis

Data are presented as mean ± standard deviation (SD) or frequencies and %. The associations between the psychological variables and post-stroke SCC were determined using Pearson product-moment correlation (r). In order to determine which factors were independently associated with SCC, multiple linear hierarchical regression analysis was used. The variables age, sex, IQ (D-NART), stroke severity (NIHSS), objective cognitive performance (OCI-index) and ADL (FAI) score were included in the first block, and then the added predictive value of each of the four psychological measures was examined in the second block (i.e., four separate covariate-adjusted models for depression, anxiety, perceived stress and fatigue; Models 1a-d). To establish which of the four psychological measures was independently associated with SCC, we tested a model that included these

four measures together combined with the aforementioned covariates (Model 2). The role of personality traits and coping style was tested in the fully adjusted model, including the background covariates, distress-related psychological factors (depression, anxiety, perceived stress and fatigue) and the personality traits and coping style measures. To minimize artifacts related to multicollinearity or model overfitting, the background covariates and distress-related psychological measures were first included in the model (forced entry) and forward stepwise procedures were used to examine the role of personality traits and coping style indices.

Regression coefficients (standardized β) are presented to indicate the strengths of the association for each of the separate variables and R^2 to describe the amount of variance explained by the model. Two-sided p-values are reported and a p-value < .05 was considered to indicate statistical significance. All analyses were performed using SPSS 22.0 software for Windows.

RESULTS

Study sample

Demographic and clinical characteristics are shown in Table 1. Most patients had a first-ever ischemic stroke and the severity of symptoms at admission to hospital was generally mild (median NIHSS score 3). The majority of patients (86%) recovered well enough to be discharged to their home environment.

Table 1. *Characteristics of the stroke sample*

Characteristic	N = 208
Age in years	64.9 ± 12.4
Males	137 (65.9%)
D-NART, IQ-estimation	95.4 ± 12.9
OCI-index [a]	5.9 ± 3.7
FAI, instrumental ADL	22.6 ± 7.8
NIHSS, stroke severity at admission: median [Q1 – Q3]	3 [2 – 5]
First-ever stroke	187 (89.9%)
Stroke side	
Left	78 (37.5%)
Right	104 (50.0%)
Not differentiated	26 (12.5%)
Length of hospital stay in days	6.7 ± 5.9
Discharge destination	
Home	179 (86.1%)
Clinical rehabilitation	29 (13.9%)

Numbers are mean ± standard deviation or number (%), unless specified otherwise. [a] Based on 185 patients who completed the neuropsychological assessment. ***Abbreviations:*** *D-NART, Dutch version of the National Adult Reading Test; FAI, Frenchay Activities Index; IQ, intelligence quotient; OCI-index, objective cognitive impairment index score; NIHSS, National Institutes of Health Stroke Scale.*

The mean CLCE scores were 3.3 ± 2.5 for SCC-c, 2.2 ± 2.3 for SCC-w and 8.6 ± 6.9 for CLCE-t. The levels of depression and anxiety were relatively low (mean HADS-D = 5.1 ± 3.8 and mean HADS-A = 4.7 ± 3.9), and the mean perceived stress (PSS-4) score was 5.0 ± 2.7. The mean fatigue (FAS) score was 24.7 ± 6.8. Descriptive statistics of the personality and coping style measures are provided in the Appendix of this chapter, Table A1. The correlations for demographic and clinical variables with CLCE scores (content, worry and total cognitive score) are shown in the Appendix Table A2. Pre-stroke IQ, the OCI-index, and ADL were significantly related to SCC and were adjusted for in the multivariate models.

Psychological factors associated with post-stroke SCC (CLCE-content)

Depressive symptoms, anxiety, perceived stress and fatigue were all significantly associated with the CLCE-c score in unadjusted analyses (see Table 2).
Multivariate linear regression analysis adjusting for age, sex, estimated IQ, stroke severity, OCI-index score and ADL in the first block and each of the distress-related psychological variables in the second block (separate analyses for each psychological variable), indicated that depression (β = 0.35), anxiety (β = 0.38), perceived stress (β = 0.39) and fatigue (β = 0.39) were associated with CLCE-c score independent of these covariates (Table 2; Models 1a-1d).

Table 2. *Associations between psychological factors and SCC (CLCE-c)*

	Unadjusted		Model 1 [a-d]		Model 2 [e]	
Independent variable	Pearson's r	p-value	β	p-value	β	p-value
HADS-depression	0.40	**<.001**	0.35 [a]	**<.001**	-0.07	.53
HADS-anxiety	0.38	**<.001**	0.38 [b]	**<.001**	**0.23**	**.02**
PSS-4, perceived stress	0.42	**<.001**	0.39 [c]	**<.001**	0.19	.05
FAS, fatigue	0.45	**<.001**	0.39 [d]	**<.001**	**0.27**	**.002**

[a-d] Separate analyses for each of the four independent variables, adjusted for age, sex, IQ-estimation (D-NART), stroke severity (NIHSS), objective cognitive impairment (OCI-index score), ADL (FAI). [e] One analysis with covariates in the first block and the independent variables being entered simultaneously in the second block. ***Abbreviations:*** *FAS, Fatigue Assessment Scale; HADS, Hospital Anxiety and Depression Scale; PSS-4, Perceived Stress Scale-short form.*

We then examined which of these four distress-related psychological measures remained independently associated with the CLCE-c score (i.e., when including these four measures together). This model explained about one-third of the variance in CLCE-c score (R^2 = 0.32; F (10, 146) = 6.99, p < .001), with anxiety (β = 0.23, p = .02) and fatigue (β = 0.27, p = .002) showing independent associations with CLCE-c score (Table 2; Model 2). The association between perceived stress and SCC was in the same direction but not statistically significant (p = .05).

The role of personality traits and coping styles in SCC

Regarding personality factors, both neuroticism (r = 0.44, p < .001) and extraversion (r = -0.19, p = .01) were correlated with the CLCE-c score in unadjusted models.

Significant correlations with SCC were also found for the coping styles avoidance (r = 0.30, p < .001) and active handling (r = -0.32, p < .001), but not for social support seeking (r = 0.01 p = .87) and palliative coping (r = 0.12, p = .11). Adjustment for background factors minimally changed the strength of these associations (data not shown).

Table 3 shows the full multivariate linear regression model examining background factors (age, sex, estimated IQ, stroke severity, OCI and ADL), distress-related psychological factors (depression, anxiety, perceived stress and fatigue), personality traits and coping styles as related to the CLCE-c score. The background covariates were included in the first block (forced entry method), depression, anxiety, perceived stress and fatigue in the second block (also using forced entry, parallel to Model 2, Table 2), and personality factors and coping styles in the third block (forward stepwise method). The overall model explained 34.2% of the variance in CLCE-c scores (R^2 = 0.34; F (11, 145) = 6.86, p < .001). Fatigue (β = 0.26, p = .003) and neuroticism (β = 0.21, p = .05) were the only psychological variables that were independently associated with CLCE-c scores, as well as the covariate objective cognitive performance (OCI-index β = 0.20, p = .03).

Table 3. *Full multivariate linear regression models examining background factors, distress-related psychological factors, personality traits and coping styles as related to SCC*

	CLCE-c		CLCE-w	
Independent variable	β	p-value	β	p-value
Age in years	0.03	.67	-0.05	.53
Sex (male)	-0.03	.67	-0.03	.69
D-NART, IQ-estimation	0.14	.12	0.17	.06
NIHSS, stroke severity at admission	-0.11	.18	-0.07	.38
OCI-index	0.20	**.03**	0.33	**.001**
FAI, instrumental ADL	-0.11	.18	-0.03	.74
HADS-depression	-0.07	.54	-0.09	.44
HADS-anxiety	0.12	.28	0.27	**.01**
PSS-4, perceived stress	0.13	.19	0.25	**.01**
FAS, fatigue	0.26	**.003**	0.16	.07
EPQ-RSS-neuroticism	0.21	**.05**	No additive value	

Multivariate models included demographics, stroke-related measures, objective cognitive performance index score, and the distress-related psychological measures (depression, anxiety, perceived stress and fatigue). Forward stepwise procedures were used to examine the additional role of personality factors and coping style. ***Abbreviations:*** *CLCE, Checklist for Cognitive and Emotional consequences following stroke; D-NART, Dutch version of the National Adult Reading Test; EPQ-RSS, Eysenck Personality Questionnaire Revised Short Scale; FAI, Frenchay Activities Index; FAS, Fatigue Assessment Scale; HADS, Hospital Anxiety and Depression Scale; IQ, intelligence quotient; NIHSS, National Institutes of Health Stroke Scale; OCI, objective cognitive impairment; PSS-4, Perceived Stress Scale-short form; UCL, Utrecht Coping List.*

Psychological variables associated with the impact of SCC (CLCE-worry)

Significant correlations with CLCE-w scores were found for depression (r = 0.35, p < .001), anxiety (r = 0.39, p < .001), perceived stress (r = 0.42, p < .001) and fatigue (r = 0.35, p < .001) (see the Appendix, Table A2). These associations remained significant when adjusting for age, sex, estimated IQ, stroke severity, OCI and ADL. As for personality factors, only neuroticism (β = 0.41, p < .001) and the coping styles avoidance (β = 0.17, p = .04) and active handling (β = -0.23, p = .01) were related to the CLCE-w scores after adjustment for the covariates.

In the full multivariate model, anxiety (β = 0.27, p = .01), perceived stress (β = 0.25, p = .01) and OCI (β = 0.33, p = .001) were independently associated with CLCE-w (overall R^2 = 0.31; F (10, 147) = 6.53, p < .001) (see Table 3).

DISCUSSION

We found that depression, anxiety, perceived stress and fatigue were all associated with SCC 3 months after stroke. When examining these distress-related psychological variables together with personality traits and coping style using multivariate analyses, fatigue and neuroticism were independently related to SCC (content component), in addition to objective cognitive performance. These findings indicate that psychological distress plays a role in SCC and that personality factors, particularly neuroticism, may be a critical factor in the association between these measures of psychological distress with SCC after stroke. This study also shows that the association between fatigue and SCC is independent of personality factors.

Unique to this study is that we explored the relationship of depression in combination with anxiety, perceived stress and fatigue with SCC. Previous studies in this area have primarily focused on depression [2, 4, 5, 12, 13, 16-18]. We confirmed the common finding that post-stroke depressive symptoms are associated with more SCC [2, 4, 5, 12, 13, 16-18]. We add to the literature that anxiety, perceived stress and fatigue are also important in post-stroke SCC. These variables are all markers of psychological distress. When examining these psychological distress-related measures conjointly in one multivariate model, we found that fatigue and anxiety were of particular relevance to SCC, independent of depression (Table 2, model 2). People with high anxiety levels are more likely to score high on personality traits associated with negative affectivity, such as neuroticism [41]. Anxiety was highly correlated with neuroticism in this study (r = 0.71). Data shown in Table 3 indicate that neuroticism may be a common background factor that partially explains the associations between depression, anxiety and perceived stress with SCC, whereas the relationship between fatigue and SCC was not explained by personality traits. These data are consistent with observations by Maaijwee et al. [17] who found associations between fatigue and SCC in univariate and multivariate models in patients evaluated > 10 years after stroke. These findings may suggest that the association between fatigue and SCC is consistent over time. We also found that avoidance coping and active handling were associated with SCC, but these

associations were not significant in the fully adjusted multivariate model. Future research is needed to determine whether post-stroke fatigue and psychological traits (such as neuroticism) are potential targets for treatment in stroke patients.

The results related to the worry/impact component of SCC were generally in the same direction as those observed for the content component of SCC. One difference was that for SCC-c, the personality trait neuroticism had additive value in explaining SCC, whereas for the worry component of SCC it did not. Anxiety and perceived stress were more important in SCC-w and this might suggest that these two variables are conceptually closely linked to worry and impact of SCC.

In addition to the psychological measures, we also found that the OCI-index, a global measure of cognitive impairment derived from a number of neuropsychological tests, was significantly related to SCC. This association has been reported in previous studies [10, 11, 13], but results have been inconsistent, including several studies that did not find correspondence between objective neuropsychological test performance and SCC [4, 12, 17]. Our findings demonstrate that psychological factors play an important role in SCC, also when measures of objective cognitive functioning are taken into account.

The present findings need to be considered in the context of a few limitations of this study. We used a cross-sectional design to explore the associations between psychological factors and SCC. Conclusions about causal pathways can therefore not be drawn. We considered using structural equation models to determine associations among higher-order factors, but elected to focus on multivariate regression models using psychological measures that can be readily implemented in clinical practice. The present results cannot be generalized to all stroke patients, since the patient sample consisted primarily of individuals with a relatively mild stroke severity (median NIHSS score 3 out of 42), a good outcome (86% of the patients was recovered well enough to be discharged home after hospitalization for stroke), and without with severe communication difficulties (patients with serve aphasia were excluded). Previous studies, however, found no associations between stroke severity or lesion size and SCC [13]. There are also several strengths of this study, including the sample size that enabled multivariate analyses of psychological variables relevant to post-stroke SCC and the differentiation between distress-related psychological measures from stable personality traits and coping styles. Furthermore, we used a comprehensive instrument for the assessment of SCC that has been specifically validated in stroke patients.

CONCLUSIONS

Anxiety, perceived stress and fatigue are strongly and independently associated with post-stroke SCC, in addition to the known relationship between depression and SCC. These associations are stronger than those of stroke-related factors with SCC. These findings therefore underscore the importance of psychological distress in SCC [2, 4]. We also found evidence that part of the interrelation between measures of psychological distress and SCC is explained by stable personality traits, particularly neuroticism, that are independent of stroke. The present study also suggests that fatigue may be an important additional target for treatment of post-stroke SCC. Future research could focus on whether interventions aimed at increasing energy levels and psychological resilience are also accompanied by an improvement in SCC. Such interventions might prove a worthwhile addition to stroke rehabilitation programs by reducing SCC and improving quality of life.

REFERENCES

1] Pendlebury ST, Mariz J, Bull L, Mehta Z, Rothwell PM. MOCA, ACE-R, and MMSE versus the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery after TIA and Stroke. Stroke. 2012;43:464-469.

2.] Lamb F, Anderson J, Saling M, Dewey H. Predictors of subjective cognitive complaint in post-acute older adult stroke patients. Arch Phys Med Rehabil. 2013;94:1747-1752.

3] Carlsson GE, Moller A, Blomstrand C. Consequences of mild stroke in persons <75 years -- a 1-year follow-up. Cerebrovasc Dis. 2003;16:383-388.

4] Duits A, Munnecom T, van Heugten C, van Oostenbrugge RJ. Cognitive complaints in the early phase after stroke are not indicative of cognitive impairment. J Neurol Neurosurg Psychiatry. 2008;79:143-146.

5] Nijsse B, van Heugten CM, van Mierlo ML, Post MW, de Kort PL, Visser-Meily JM. Psychological factors are associated with subjective cognitive complaints 2 months post-stroke. Neuropsychol Rehabil. 2017;27:99-115.

6] Wendel K, Risberg J, Pessah-Rasmussen H, Stahl A, Iwarsson S. Long-term cognitive functional limitations post stroke: Objective assessment compared with self-evaluations and spouse reports. Int J Rehabil Res. 2008;31:231-239.

7] McKevitt C, Fudge N, Redfern J, Sheldenkar A, Crichton S, Rudd AR, et al. Self-reported long-term needs after stroke. Stroke. 2011;42:1398-1403.

8] van Rijsbergen MW, Mark RE, de Kort PL, Sitskoorn MM. Subjective cognitive complaints after stroke: A systematic review. J Stroke Cerebrovasc Dis. 2014;23:408-420.

9] Davis AM, Cockburn JM, Wade DT, Smith PT. A subjective memory assessment questionnaire for use with elderly people after stroke. Clin Rehabil. 1995;9:238-244.

10] Narasimhalu K, Wiryasaputra L, Sitoh YY, Kandiah N. Post-stroke subjective cognitive impairment is associated with acute lacunar infarcts in the basal ganglia. Eur J Neurol. 2013;20:547-551.

11] Van Heugten C, Rasquin S, Winkens I, Beusmans G, Verhey F. Checklist for cognitive and emotional consequences following stroke (CLCE-24): Development, usability and quality of the self-report version. Clin Neurol Neurosurg. 2007;109:257-262.

12] Winkens I, Van Heugten CM, Fasotti L, Wade DT. Reliability and validity of two new instruments for measuring aspects of mental slowness in the daily lives of stroke patients. Neuropsychol Rehabil. 2009;19:64-85.

13] Xiong YY, Wong A, Mok VC, Tang WK, Lam WW, Kwok TC, et al. Frequency and predictors of proxy-confirmed post-stroke cognitive complaints in lacunar stroke patients without major depression. Int J Geriatr Psychiatry. 2011;26:1144–1151.

14] van Rijsbergen MW, Mark RE, de Kort PL, Sitskoorn MM. Prevalence and profile of poststroke subjective cognitive complaints. J Stroke Cerebrovasc Dis. 2015;24:1823-1831.

15] van Rijsbergen MW, Mark RE, Kop WJ, de Kort PL, Sitskoorn MM. The role of objective cognitive dysfunction in subjective cognitive complaints after stroke. Eur J Neurol. 2017;24:475-482.

16] Aben L, Ponds RW, Heijenbrok-Kal MH, Visser MM, Busschbach JJ, Ribbers GM. Memory complaints in chronic stroke patients are predicted by memory self-efficacy rather than memory capacity. Cerebrovasc Dis. 2011;31:566-572.

17] Maaijwee NA, Schaapsmeerders P, Rutten-Jacobs LC, Arntz RM, Schoonderwaldt HC, van Dijk EJ, et al. Subjective cognitive failures after stroke in young adults: Prevalent but not related to cognitive impairment. J Neurol. 2014;261:1300-1308.

18] Martin C, Dellatolas G, Viguier D, Willadino-Braga L, Deloche G. Subjective experience after stroke. Appl Neuropsychol. 2002;9:148-158.

19] Galligan NG, Hevey D, Coen RF, Harbison JA. Clarifying the associations between anxiety, depression and fatigue following stroke. J Health Psychol. 2016;21:2863-2871.

20] Comijs HC, Deeg DJ, Dik MG, Twisk JW, Jonker C. Memory complaints; the association with psycho-affective and health problems and the role of personality characteristics. A 6-year follow-up study. J Affect Disord. 2002;72:157-165.

21] Pearman A, Storandt M. Predictors of subjective memory in older adults. J Gerontol B Psychol Sci Soc Sci. 2004;59:P4-6.

22] Aben I, Denollet J, Lousberg R, Verhey F, Wojciechowski F, Honig A. Personality and vulnerability to depression in stroke patients: A 1-year prospective follow-up study. Stroke. 2002;33:2391-2395.

23] van Rijsbergen MW, Mark RE, de Kort PL, Sitskoorn MM. The COMPlaints After Stroke (COMPAS) study: Protocol for a Dutch cohort study on poststroke subjective cognitive complaints. BMJ Open. 2013;3:e003599.

24] de Jonghe JF, Schmand B, Ooms ME, Ribbe MW. [Abbreviated form of the informant questionnaire on cognitive decline in the elderly]. Tijdschr Gerontol Geriatr. 1997;28:224-229.

25] Brott T, Adams HP, Jr., Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: A clinical examination scale. Stroke. 1989;20:864-870.

26] Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand. 1983;67:361-370.

27] Sagen U, Vik TG, Moum T, Morland T, Finset A, Dammen T. Screening for anxiety and depression after stroke: Comparison of the Hospital Anxiety and Depression Scale and the Montgomery and Asberg Depression Rating Scale. J Psychosom Res. 2009;67:325-332.

28] Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression scale (HADS) in different groups of Dutch subjects. Psychol Med. 1997;27:363-370.

29] Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24:385-396.

30] Warttig SL, Forshaw MJ, South J, White AK. New, normative, English-sample data for the short form Perceived Stress Scale (PSS-4). J Health Psychol. 2013;18:1617-1628.

31] Michielsen HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: The fatigue assessment scale. J Psychosom Res. 2003;54:345-352.

32] Mead G, Lynch J, Greig C, Young A, Lewis S, Sharpe M. Evaluation of fatigue scales in stroke patients. Stroke. 2007;38:2090-2095.

33] Sanderman R, Arrindell WA, Ranchor A, Eysenck HJ, Eysenck SBG. [Measurement of personality traits using the Eysenck Personality Questionnaire: A manual]. Groningen: Noordelijk Centrum voor Gezondheidsvraagstukken, Rijksuniversiteit Groningen; 1995.

34] Sato T. The Eysenck Personality Questionnaire brief version: Factor structure and reliability. J Psychol. 2005;139:545-552.

35] Sanderman R, Ormel J. [The

Utrecht Coping List (UCL): Validity and reliability]. Gedrag Gezond. 1992;20:32-37.
36 Schreurs PJG, Van de Willege G, Brosschot JF, Tellegen B, Graus GMH. [The Utrechtse Coping List: UCL manual]. Utrecht: Swets en Zeitlinger; 1993.
37] van den Akker M, Buntinx F, Metsemakers JF, Knottnerus JA. Marginal impact of psychosocial factors on multimorbidity: Results of an explorative nested case-control study. Soc Sci Med. 2000;50:1679-1693.
38] Davis JJ, Axelrod BN, McHugh TS, Hanks RA, Millis SR. Number of impaired scores as a performance validity indicator. J Clin Exp Neuropsychol. 2013;35:413-420.
39] Schmand B, Bakker D, Saan R, Louman J. [The Dutch adult reading test: A measure of premorbid intelligence]. Tijdschr Gerontol Geriatr. 1991;22:15-19.
40] Holbrook M, Skilbeck CE. An activities index for use with stroke patients. Age Ageing. 1983;12:166-170.
41] Jylha P, Isometsa E. The relationship of neuroticism and extraversion to symptoms of anxiety and depression in the general population. Depress Anxiety. 2006;23:281-289.

CHAPTER 6
APPENDIX

Table A1. *Descriptives of personality traits and coping styles*

	Mean ± SD
EPQ-RSS – neuroticism	3.4 ± 3.0
EPQ-RSS – extraversion	6.7 ± 3.1
UCL – avoidance	6.2 ± 1.7
UCL – active handling	13.6 ± 2.9
UCL – seeking social support	10.6 ± 2.6
UCL – palliative reaction	4.4 ± 1.3

Abbreviations: *EPQ-RSS, Eysenck Personality Questionnaire Revised Short Scale; SD, standard deviation; UCL, Utrecht Coping List.*

Table A2. *Correlations for demographic, clinical and psychological variables with CLCE scores*

Independent variables	CLCE-c		CLCE-w		CLCE-t	
	Pearson's r	p-value	Pearson's r	p-value	Pearson's r	p-value
Demographic and clinical measures						
Age in years	0.08	.23	-0.02	.76	0.05	.49
Sex (male)	-0.12	.09	-0.11	.11	-0.12	.09
IQ-estimation (D-NART)	-0.15	**.03**	-0.14	.05	-0.15	**.03**
NIHSS score at admission	-0.01	.92	0.02	.83	<0.001	.99
OCI-index	0.25	**.001**	0.28	**<.001**	0.27	**<.001**
FAI, instrumental ADL	-0.23	**.001**	-0.14	**.05**	-0.21	**.003**
Psychological measures						
HADS-depression	0.40	**<.001**	0.35	**<.001**	0.40	**<.001**
HADS-anxiety	0.38	**<.001**	0.39	**<.001**	0.40	**<.001**
PSS-4, perceived stress	0.42	**<.001**	0.42	**<.001**	0.44	**<.001**
FAS, fatigue	0.45	**<.001**	0.35	**<.001**	0.44	**<.001**
EPQ-RSS – neuroticism	0.44	**<.001**	0.43	**<.001**	0.46	**<.001**
EPQ-RSS – extraversion	-0.19	**.01**	-0.14	.06	-0.18	**.02**
UCL – avoidance	0.30	**<.001**	0.21	**.01**	0.28	**<.001**
UCL – active handling	-0.32	**<.001**	-0.29	**<.001**	-0.32	**<.001**
UCL – seeking social support	0.01	.87	0.07	.36	0.04	.59
UCL – palliative reaction	0.12	.11	0.09	.24	0.12	.12

Abbreviations: *CLCE, Checklist for Cognitive and Emotional consequences following stroke, content, worry or total cognitive score; D-NART, Dutch version of the National Adult Reading Test; EPQ-RSS, Eysenck Personality Questionnaire Revised Short Scale; FAI, Frenchay Activities Index; FAS, Fatigue Assessment Scale; HADS, Hospital Anxiety and Depression Scale; NIHSS, National Institutes of Health Stroke Scale; OCI, objective cognitive impairment; PSS-4, Perceived Stress Scale-short form; UCL, Utrecht Coping List.*

CHAPTER 7

COURSE AND PREDICTORS OF SUBJECTIVE COGNITIVE COMPLAINTS DURING THE FIRST 12 MONTHS AFTER STROKE

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ABSTRACT

Objective: Subjective cognitive complaints (SCC) are common after stroke. How SCC evolve over time and which factors predict whether patients will continue to experience SCC, is unknown. This study documents the prevalence and course of SCC in the first year after stroke and determines which patient characteristics in the first 3 months predict subsequent SCC at 1-year follow-up.

Methods: Using a longitudinal design, 155 patients (mean age 64.0 ± 11.9 years; 69.7% men) were assessed at 3 and 12 months after stroke. SCC were evaluated using the Checklist for Cognitive and Emotional consequences following stroke (CLCE) inventory (content component, CLCE-c, and worry component, CLCE-w). Potential predictors of 12 months SCC included demographics, stroke severity, objective cognitive impairment, psychological factors (depression, anxiety, perceived stress, fatigue, personality traits, coping style), and activities of daily living assessed at 3 months post stroke. Multivariate hierarchical linear regression analyses were used to determine predictors of SCC at 12 months post-stroke.

Results: CLCE-c scores remained stable over time (3.3 ± 2.4 at 3 months versus 3.3 ± 2.6 at 12 months). Independent predictors of SCC at 12 months were baseline CLCE-c (standardized β = 0.54) and perceived stress (standardized β = 0.23) for SCC-content and baseline CLCE-w (standardized β = 0.57) and depressive symptoms (standardized β = 0.23) for SCC- worry.

Conclusions: Patients who report SCC at 3 months after stroke are likely to continue having these complaints at 1 year follow-up. Perceived stress and depressive symptoms additionally increase the likelihood of having SCC at 12 months, independent of SCC at 3 months post-stroke. Rehabilitation programs that target reduction of stress and depression in the first months after stroke might reduce sustained SCC and improve well-being.

INTRODUCTION

Subjective cognitive complaints (SCC) are common after stroke, with prevalence estimates ranging between 28.6 [1] and 92.0% [2] (see also Chapter 2 [3]). Post-stroke SCC are associated with patient characteristics, including poor objective cognitive performance (OCP) [4-9] and psychological factors such as depression, anxiety, perceived stress [9-11] and coping style [11], although the results regarding the magnitude of these associations are mixed (see also Chapter 2 [3,] Chapter 5 [12] and Chapter 6). To date, most of the studies on post-stroke SCC rely on cross-sectional designs and as such provide limited information about how SCC evolve over time and which factors are of predictive value for long-term SCC.

Neuropsychological research has demonstrated that approximately 70% of patients display stable OCP over time [13], while both deterioration (estimates ranging between 7% and 41%) [14, 15] and improvements (range between 20% - 30%) [13, 16] have also been documented. These changes in OCP may have effects on trajectories of post-stroke SCC. We previously documented that global objective impairment in cognitive functioning is associated with SCC 3 months after stroke (Chapter 4 [12]), which is consistent with other studies [4, 7-9]. In contrast to the general trends for stable cognitive function over time after stroke, Tinson and Lincoln [17] found that patients reported more SCC (especially memory-related) at 7 months compared to at 1 month after stroke. It remains unknown, however, if this is also true for other SCC than those related to memory, which factors are associated with increased SCC over time, and whether baseline variables can be identified that increase the risk of having SCC in the long term.

In the present longitudinal study, we examined (1) whether and how SCC changes during the first year after stroke, and (2) whether stroke severity (at time of admission), OCP and/or psychological characteristics at 3 months are predictive of SCC at 1 year follow-up.

METHODS

Design and procedure

The current longitudinal study reports data from the COMplaints After Stroke (COMPAS) study (see Chapter 3 [18]). Between October 2009 and August 2012, patients were recruited from the Elisabeth-TweeSteden Hospital and the Maxima Medical Center, The Netherlands. The medical ethics committees of these institutions approved the protocol and written informed consent was obtained from all individuals participating in this study.

Participants were invited to one of the hospitals for the assessment of SCC and neuropsychological test performance at 3 (mean 3.3 ± 0.5) and 12 (12.9 ± 0.9) months after stroke. Psychological questionnaires were completed at home and returned by mail. A reminder was sent when questionnaires were not returned within 2 weeks.

Participants

Patients with a clinical diagnosis of stroke (either ischemic or hemorrhagic, first-ever or recurrent) and aged ≥ 18 years were eligible for the study. Exclusion criteria were: premorbid health problems interfering with cognitive functioning (e.g. cognitive decline, as defined by a score > 3.6 on the short version of the Informant Questionnaire on Cognitive Decline in the Elderly [19]), life-threatening progressive diseases (e.g., cancer or kidney failure), a recent history of psychopathology, and/or severe communication difficulties.

Four hundred and thirty-five patients were eligible at 3 months, of whom 208 (47.8%) agreed to participate and had a first SCC assessment (see Figure 1). Non-participants (i.e., patients who were ot interested (N = 123), or could not be approached in time for the research assessments (N = 101), and those who had no SCC evaluation at 3-months baseline (N = 3), did not differ from participants with regard to stroke type (93.0% versus 94.7% had an ischemic stroke, $\chi^2(1) = 0.58$, p = .45). However, patients who were not included in the COMPAS project more often had a left-sided lesion (56.5% versus 42.9%, $\chi^2(1) = 7.1$, p = .01) and were less severely affected by their stroke at time of admission (National Institutes of Health Stroke Scale, NIHSS [20], median NIHSS score = 2, interquartile range (IQR) = 1 - 4 versus median score = 3, IQR = 2 - 5; U = 18088.5, p = .03). Non-participants were also older (69.6 ± 12.4 versus 64.7 ± 12.4 years, t(433) = -4.1, p < .001) and were more often female (44.5% versus 34.1%, $\chi^2(1) = 4.9$, p = .03).

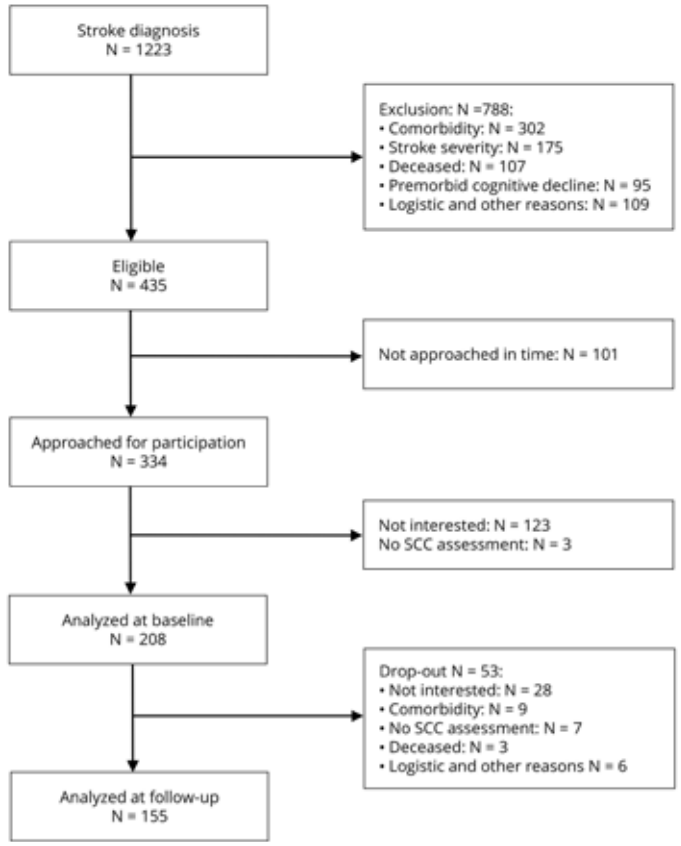
From the 208 patients tested at baseline (3 months), 155 (74.5%) were available for follow-up at 12 months with a second SCC assessment. Participants who were lost to follow-up (N = 53, see Figure 1) did not differ from those with 12-month data regarding most clinical and demographic measures (see Table A1 in the Appendix of this chapter). However, more women than men dropped-out (33.8% versus 21.2%, $\chi^2(1) = 3.9$, p = .05) and those lost to follow-up had more objective cognitive impairment (OCI) at baseline (OCI-index-score: 7.0 ± 4.0 versus 5.6 ± 3.5, t(182) = 2.1, p = .03) than those who returned for the 12-months measurement.

Measures

Outcome variable: subjective cognitive complaints

SCC were assessed using the Checklist for Cognitive and Emotional consequences following stroke (CLCE) [7] inventory. The CLCE is a semi-structured interview exploring post-stroke cognitive, emotional and behavioral complaints. Thirteen of the 24 items focus on self-reported cognitive problems and were used in the present study. Each item was scored on presence and interference in daily life: 0 (SCC not present), 1 (presence uncertain), 2 (present, but not affecting daily life), 3 (present and negatively affecting daily life).

Figure 1. *Flow chart of the study population*



Abbreviation: *SCC, subjective cognitive complaints*

Based on previous studies, two components of SCC were examined: a *content* component referring to the nature of cognitive difficulties (CLCE-c), and an impact or *worry* component describing whether individuals reported that their specific content-related SCC had an impact on their daily lives (CLCE-w) (see also Chapters 2-6 [3, 12, 18, 21]). The CLCE-c score was used as the primary outcome index of SCC and defined as the number of SCC present irrespective of whether these interfered with daily life. It was calculated by dichotomizing each item score into 'absent' (original item score 0) and 'present' (item score 1 through 3) and summing the items (score range CLCE-c score = 0-13). In addition, the CLCE-w score, defined as the number of SCC having an impact on daily life, was calculated by dichotomizing each item into 'absence of interference' (item score 0 through 2) or 'presence of interference' (item score 3) and summed over the 13 items (range CLCE-w score = 0-13). We have previously used this procedure to quantify SCC using the CLCE (Chapters 4 [21], 5 [12] and 6). The total CLCE score was also calculated (CLCE-t) by summing the original item scores (range 0-39).

The CLCE has previously been validated in stroke patients [7]. The internal consistency is good (Cronbach's α = 0.81 based on the 22 standardized items) [7]. In the present study Cronbach's α was 0.71 for CLCE-c, 0.75 for CLCE-w, and 0.74 for CLCE-t at 3 months after stroke.

Predictor variables

Demographic and clinical characteristics

Demographics and stroke-related measures were obtained from the patients' medical records. Stroke characteristics (type, side and stroke severity, assessed by NIHSS) and destination of discharge (home versus rehabilitation center) were recorded during the hospitalization phase. The Dutch version of the National Adult Reading Test (D-NART) [22] was used to estimate the pre-stroke intelligence quotient (IQ).

Objective cognitive performance

Standardized neuropsychological tests were used to calculate the objective cognitive impairment (OCI) index score (i.e., total number of impaired test scores, range 0-20). The OCI-index was previously used in Chapter 5 [12] to quantify the association between objective cognitive performance with SCC.

Psychological distress variables

The Hospital Anxiety and Depression Scale (HADS) [23] was used to assess symptoms of depression (7 items, HADS-D) and anxiety (7 items, HADS-A). The total score for both subscales ranges between 0 and 21, with higher scores indicating more symptoms. The HADS has good psychometric properties (Cronbach's α > 0.80) and is used as a screening instrument after stroke [24, 25].

The Perceived Stress Scale-short form (PSS-4) [26] was used to measure the degree to which recent life situations are perceived as stressful. The total score ranges between 0 and 16, with a higher score indicating more perceived stress. The psychometric properties of the PSS-4 are satisfactory (Cronbach's α ranging between 0.60 and 0.82) [27].

The Fatigue Assessment Scale (FAS) [28] (10 items) was used as a measure of fatigue. The total score ranges between 10 and 50 (higher scores indicating more fatigue). The FAS is a useful measure of post-stroke fatigue because of its adequate face validity, feasibility, high test-retest reliability and high construct validity [29].

Personality traits

Neuroticism and extraversion were assessed using the two corresponding subscales of the Eysenck Personality Questionnaire Revised Short Scale (EPQ-RSS [30]). Total scores range from 0 to 12 with higher scores indicating more characteristics of the specific personality trait. The EPQ-RSS has demonstrated good internal consistency, test-retest reliability and concurrent validity [31].

Coping style

The abbreviated version of the Utrecht Coping List (UCL) [32-34] contains 15 items from which four styles are derived, including: active, seeking social support, avoiding, and palliative coping. Total scores are computed for each domain with higher scores indicating a greater tendency to adopt the particular coping style. The UCL has moderate to good internal consistency and test-retest reliability [35].

Activities of daily living (ADL)

The Frenchay Activities Index (FAI) [36] was used to measure instrumental ADL. It comprises 15 items evaluating the ability to perform complex activities like housekeeping, hobbies, shopping, paid work and driving. Items are rated on a 4-point scale ranging from 0 (never) to 3 (a higher frequency or higher level of the activity). Total scores vary between 0 and 45, with higher scores indicating a more active lifestyle. The FAI is a good stroke-specific instrument with good internal consistency, validity and reliability [37, 38].

Statistical Analysis

Data are presented as mean ± standard deviation (SD) or frequencies and %. Changes in SCC measures over time were evaluated using paired samples t-tests comparing mean CLCE-c, CLCE-w and CLCE-t scores at 3 and 12 months. The stability of SCC was also examined using correlation analysis (Pearson's r for 3 and 12 months measures).

In addition, change patterns in individual patients' CLCE scores were explored by displaying the frequency of patients whose scores increased or decreased by at least 1 SD between their baseline and follow-up assessment (i.e., a CLCE change score > 1). To further display the pattern of individual changes, each patient was categorized based on a quintile CLCE-c distribution at baseline: 1 ('no or minimal SCC': CLCE-c score = 0-1), 2 (CLCE-c = 2), 3 (CLCE-c = 3), 4 (CLCE-c = 4-5) and 5 ('high SCC': CLCE-c score = 6-13). The number of patients changing from CLCE-c category over time was then displayed. The reliable change index (RCI) was computed using the formula developed by Jacobson and Truax to identify how many patients displayed a clinically significant change [39].

To determine predictors of change in SCC, multiple linear hierarchical regression analyses were performed (separate analyses for CLCE-c, CLCE-w and CLCE-t scores) adjusting for baseline variables. For every outcome variable (CLCE-c, CLCE-w and CLCE–t), two models were explored, one *without* the corresponding CLCE measure at baseline (Model 1) and one *with* adjustment for baseline CLCE score (Model 2). The first model included demographic and clinical characteristics (age, sex, IQ-estimation, NIHSS score; block 1), OCI-index score (block 2), psychological distress variables (depression, anxiety, perceived stress, fatigue; block 3), personality traits and coping style (block 4) and ADL-functioning (block 5). In the second model, an extra block was added including the baseline CLCE score (block 1). The baseline CLCE score, demographic characteristics, stroke severity and OCI were forced-

entered into the model. Forward stepwise procedures were used to examine the role of the other variables. Regression coefficients (standardized β) are presented to indicate the strengths of the associantion for each of the seperate variables.

Two-sided p-values are reported and a p-value < .05 was considered to indicate statistical significance. All analyses were performed using SPSS 22.0 software for Windows.

RESULTS

Patient characteristics

Table 1 displays the characteristics of the participants measured at baseline (3 months) (mean age 64.0 ± 11.9; 69.7% men). Most patients had a first-ever ischemic stroke and the severity of symptoms at admission to hospital was generally mild (median NIHSS score 3). The majority of patients (85.8%) recovered well enough to be discharged to their home environment. From the 155 participants analyzed at baseline and follow-up, 22 (14.2%) had an intermittent event during the follow-up period, including: a transient ischemic attack (TIA, N = 1), another stroke (N = 2), and a hospital admission for other reasons, for example, hip replacement or cardiac problems (N = 19).

Table 1. *Baseline demographic and clinical characteristics*

Characteristic	N = 155
Age in years, mean ± SD	64.0 ± 11.9
Males, n (%)	108 (69.7%)
D-NART, IQ-estimation, mean ± SD (N=150)	96.0 ± 11.9
First-ever stroke, n (%)	140 (90.3%)
Ischemic stroke, n (%)	146 (94.2%)
Stroke side	
Left, n (%)	63 (40.6%)
Right, n (%)	72 (46.5%)
Not differentiated, n (%)	20 (12.9%)
NIHSS, Severity of stroke at admission, median [Q1 – Q3]	3 [2 – 5]
Length of hospital stay in days, mean ± SD	6.6 ± 5.8
Discharge destination	
Home, n (%)	133 (85.8%)
Clinical rehabilitation, n (%)	22 (14.2%)

Abbreviations: *D-NART, Dutch version of the National Adult Reading Test; IQ, Intelligence Quotient; NIHSS, National Institutes of Health Stroke Scale; SD, Standard Deviation.*

Course of subjective cognitive complaints

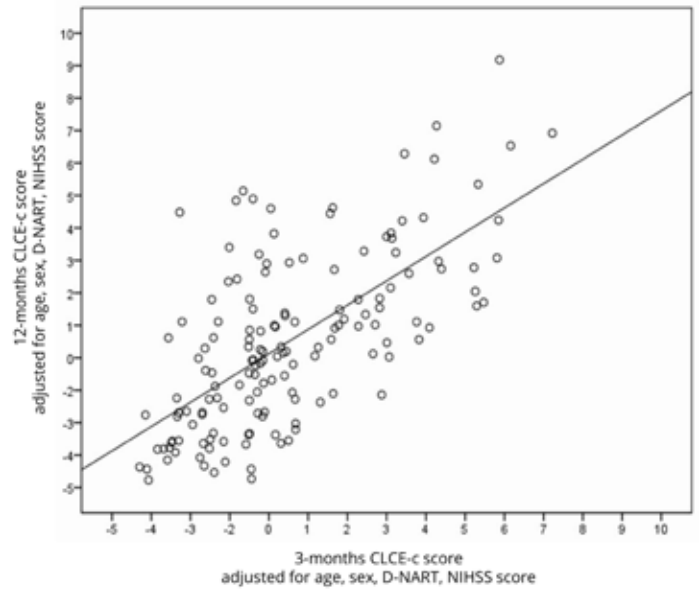
At the group level, the CLCE-c scores remained stable from the 3-months baseline assessment to the 12-months follow-up (t(154) < 0.01, p > .99) (Table 2). The 3-months and 12-months CLCE-c scores were also significantly correlated with each other (r = 0.66, p < .001) (Figure 2a).

Table 2. *Change over time in subjective and objective cognitive functioning, psychological distress, fatigue and ADL*

	3 months	12 months	p-value
CLCE-c	3.3 ± 2.4	3.3 ± 2.6	>.99
CLCE-w	1.9 ± 2.2	2.1 ± 2.5	.28
CLCE-t	8.5 ± 6.6	8.7 ± 7.6	.63
OCI-index	5.6 ± 3.5	5.4 ± 3.9	.05
HADS-depression	4.9 ± 3.7	4.4 ± 3.6	.08
HADS-anxiety	4.6 ± 3.8	4.3 ± 2.8	.44
PSS-4, perceived stress	4.9 ± 2.7	4.4 ± 3.6	**.01**
FAS, fatigue	24.6 ± 6.7	23.7 ± 6.9	**.05**
FAI, instrumental ADL	22.7 ± 8.1	24.1 ± 7.0	**.001**

Due to missing values, 133 patients were analyzed on OCI, 125 on the HADS, 124 on the PSS-4, 119 on the FAS and 149 on the FAI. ***Abbreviations:*** *ADL, activities of daily living; CLCE, Checklist for Cognitive and Emotional consequences following stroke, content, worry, total score; FAI, Frenchay Activities Index; FAS, Fatigue Assessment Scale; HADS, Hospital Anxiety and Depression Scale; IQ, Intelligence Quotient; OCI, objective cognitive impairment; PSS-4, Perceived Stress Scale-short form.*

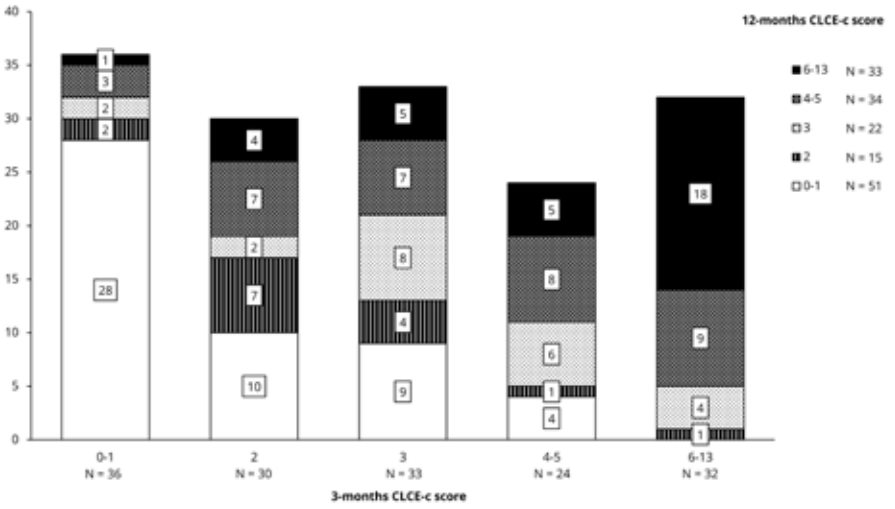
Figure 2a. *Correlation between 3- and 12-months CLCE-c scores, adjusted for the effects of age, sex, IQ-estimation and stroke severity*



Adjustments for age, sex, D-NART (IQ-estimation) and NIHSS score were performed using linear regression analyses. ***Abbreviations:*** *CLCE-c, Checklist for Cognitive and Emotional consequences following stroke, content score; D-NART, Dutch version of the National Adult Reading Test; NIHSS, National Institutes of Health Stroke Scale.*

At the individual patient level, more than half of the patients (N = 88, 56.8%) had a stable CLCE-c score (< 1 SD change i.e., 0 or maximum 1 point difference) over time. Figure 2b depicts the number of patients who were classified in each of the five CLCE-c categories (scores 0-1; 2; 3; 4-5; and 6-13) at baseline (categories based on quintiles of the baseline CLCE-c distribution) and whether and how they changed from category at follow-up. Sixty-nine patients (44.5%) remained in the same category, 38 (24.5%) moved to a higher category at follow-up (i.e., more SCC) and 48 (31.0%) moved to a lower category at follow-up (i.e., less SCC). However, RCI analyses indicated that the degree of change at the individual level was small: only 8 (5.2%) patients worsened and 3 (1.9%) improved using RCI criteria.

Figure 2b. *Change in SCC-c from baseline tot follow-up (CLCE-c score)*



The X-as represents the number of patients in each CLCE-c score category at baseline (3-months). The coloured blocks represent the number of patients in each category at follow-up (12-months). For example, 36 patients had a 0 or 1 CLCE score at baseline (i.e. the sum of the coloured blocks in the '0-1' category), of whom 28 patients kept having this score at follow-up, 2 patients reported 1 point increase (total score 2) and were classified in the '2' category, 2 patients had an increase of 2 points (total score 3) and were classified in the '3' category, 3 patients changed to the '4-5' category and 1 changed to the '6-13' category at follow-up. ***Abbreviation:*** *CLCE-c, Checklist for Cognitive and Emotional consequences following stroke, content score.*

A similar pattern was found for the CLCE-w score, with a change from 1.9 ± 2.2 to 2.1 ± 2.5 (t(154) = -1.10, p = .28) from 3 to 12 months, a high correlation of the CLCE-w scores over time (r = 0.65, p < .001), and 100 (64.5%) patients showing stable (0-1 point change) CLCE-w scores. According to the RCI, significant deterioration was seen in 8 (5.2%) and improvement in 6 (3.9%) patients.

Predictive value of baseline characteristics for SCC at 12-months post-stroke

As shown in Table 3, unadjusted associations between the 3-months baseline measures with 12-months follow-up CLCE-c scores were significant (p < .05) for OCI-index score (r = 0.20), depression (r = 0.36), anxiety (r = 0.35), perceived stress (r = 0.49), fatigue (r = 0.40), neuroticism (r = 0.47), dimensions of coping (avoidant r = 0.29, active r = -0.23 and palliative r = 0.19) and ADL (r = -0.20). The strongest association was found with baseline CLCE-c score (r = 0.66, p < .001).

Multivariate models (Table 3) indicated that OCI (β = 0.19), perceived stress (β = 0.25), fatigue (β = 0.16) and neuroticism (β = 0.25) at 3 months were independently associated with CLCE-c score at 12-months follow-up (covariate-adjusted Model 1). After additionally including the 3-months baseline CLCE-c score (Model 2), only perceived stress (β = 0.23) remained predictive of CLCE-c at 12-months follow-up, in addition to the baseline CLCE score (β = 0.54, p < .001).

Table 3. *Associations between 3-months characteristics and 12-months subjective cognitive complaints*

	Correlations		Multiple Regression			
			Model 1		Model 2	
	Pearson's r	p-value	Standardized β	p-value	Standardized β	p-value
Block 1						
CLCE-c	0.66	**<.001**	Not entered		0.54	**<.001**
Block 2						
Age	-0.08	.35	-0.07	.39	-0.08	.26
Sex (male)	-0.09	.29	-0.04	.60	-0.01	.84
D-NART, IQ-estimation	-0.15	.07	0.07	.45	-0.02	.78
NIHSS, stroke severity	-0.13	.88	-0.04	.63	-0.01	.94
Block 3						
OCI-index score	0.20	**.02**	0.19	**.05**	0.07	.41
Block 4						
HADS-depression	0.36	**<.001**	†		†	
HADS-anxiety	0.35	**<.001**	†		†	
PSS4, perceived stress	0.49	**<.001**	0.25	**.02**	0.23	**.003**
FAS, fatigue	0.40	**<.001**	0.16	.08	†	
Block 5						
EPQ-RSS, neuroticism	0.47	**<.001**	0.25	**.01**	†	
EPQ-RSS, extraversion	-0.10	.24	†		†	
UCL-avoidance	0.29	**<.001**	†		†	
UCL-active handling	-0.23	**.01**	†		†	
UCL-seeking social support	0.05	.54	†		†	
UCL-palliative reaction	0.19	**.02**	†		†	
Block 6						
FAI, instrumental ADL	-0.20	**.01**	†		†	

Model 1: *CLCE-c baseline score (at 3 months) not included.* ***Model 2:*** *CLCE-c baseline score included. Variables in block 1 - 3 were entered using the enter procedure. In block 4-6, a forward procedure was used.* ***Sign:*** *† Variables that were removed from the analysis using a forward procedure.* ***Abbreviations:*** *ADL, activities of daily living; CLCE-c, Checklist for Cognitive and Emotional consequences following stroke, content score; D-NART, Dutch version of the National Adult Reading Test; EPQ-RSS, Eysenck Personality Questionnaire Revised Short Scale; FAI, Frenchay Activities Index; FAS, Fatigue Assessment Scale; HADS, Hospital Anxiety and Depression Scale; IQ, intelligence quotient; NIHSS, National Institutes of Health Stroke Scale; OCI, objective cognitive impairment; PSS-4, Perceived Stress Scale-short form; UCL, Utrecht Coping List.*

The results for CLCE-w showed a similar pattern as for CLCE-c (see Table A2 in the Appendix), the only difference being that in the multivariate regression models for CLCE-w, baseline depression (β = 0.23) (instead of perceived stress) had additional predictive value for CLCE-w at 12 months.

We also compared individuals who improved in SCC and those who had worsening in SCC with patients with stable SCC. Patients reporting improvements in SCC (i.e., a > 1 point decrease in CLCE-c scores from 3- to 12-months) did not differ from those with stable scores at 3 and 12 months on any of the stroke-related or psychological measures. However, those with worsening of SCC (a > 1 point increase in CLCE-c score) at follow-up reported overall an increase in depression and anxiety symptoms and a decrease in instrumental ADL over time. No consistent associations were found between changes in OCI and improvements or worsening in SCC (data not shown).

DISCUSSION

We found that in general, SCC remained stable from 3 to 12 months after stroke. At the individual level, approximately half of the patients (56.8%) had stable SCC over time (i.e., CLCE changes of 1 point or less), and only 11 patients displayed clinically significant changes over time using RCI analysis (8 worsened and 3 improved). Consequently, the presence of SCC at follow-up was primarily predicted by 3-months baseline SCC. In addition, independent predictive value was found for perceived stress (for CLCE-c) and depression (for CLCE-w). These findings suggest that patients with SCC at 3 months after stroke are also likely to have these complaints at 1 year after stroke, and that perceived stress and depressive symptoms are primary psychological characteristics that may influence the course of SCC over time.

The increase in SCC over time after stroke as observed in this study is smaller than changes reported by Tinson and Lincoln [17]. These investigators suggested that increased SCC over time could be related to a heightened awareness of and/or confrontation with cognitive difficulties in daily life [17]. We found that the patients with more SCC at 12 than at 3 months also showed a larger increase in self-reported anxiety symptoms compared to patients with stable SCC. Although this might be related to changes in awareness and/or ADL, the reason of the observed increase in anxiety symptoms can however not be derived from the data in the present study.

Whether and how much change in SCC occurs after stroke, might depend on the type of SCC assessed. We aggregated SCC over multiple cognitive domains, whereas Tinson and Lincoln [17] focused on memory-related SCC. Furthermore, the timing of assessments after stroke may be a factor to consider as we evaluated patients at 3 and 12 months after stroke, while Tinson and Lincoln [17] assessed them at 1 and 7 months post-stroke. Changes in SCC might occur mainly in the first couple of months after stroke, a period of emotional and physical adjustment (e.g., recovering from and/or dealing with consequences of stroke and changes in daily life functioning, being aware of having survived a stroke). Future longitudinal research might evaluate patients over a longer period (e.g., > 1 year) after stroke to explore changes in SCC in more detail.

The role of objective cognitive performance measured by neuropsychological testing in SCC requires specific attention. Consistent with prior research, we previously documented that a global index of impaired OCP is cross-sectionally related to SCC in patients assessed at 3 months after stroke (Chapter 5 [12]). Research has shown that improvements in OCP is seen in about 20-30% of the patients in the year following stroke [13, 16] and the present study supports this trend (see Table 2). Based on this background, it would have been plausible that the improvements in OCP were accompanied by a reduction in SCC, but no support for such an association was found. Another aspect is that we considered SCC as an outcome variable in this study, but from a different perspective, SCC could also be a considered as a potential risk indicator for future impairments in OCP. Van Heugten et al. [7] reported that SCC at 6 months post-stroke predicted OCP measured using neuropsychological screening tests at 12 months follow-up. We therefore explored whether SCC at 3 months had predictive value for OCP at 12 months post-stroke. In contrast to Van Heugten et al. [7], we did not find that SCC was predictive of future OCP. In the present study, OCP and age at 3 months proved to be more important than SCC in predicting future OCP (Table A3 in the Appendix). Methodological differences between our study and Van Heugten et al. [7] might partially explain the inconsistent findings, including: differences in measurement times (3 and 12 months versus 6 and 12 months) and that we adjusted for demographic, clinical and psychological variables (Van Heugten et al. [7] adjusted only for sex).

A few limitations of the present study need to be considered. The study sample consisted mainly of patients with a mild stroke (median NIHSS score 3 out of 42), with a relatively good outcome (85.8% of the patients recovered well enough to be discharged home), and without severe communication difficulties (patients with severe aphasia were excluded). This makes generalizability of the findings to the stroke population as a whole, difficult. The follow-up period (12 months after stroke) does not allow extrapolation to the long-term course of SCC and its related variables. Future research with more SCC assessments during several years after the event may give more insight into the evolution of post-stroke SCC over time. Because the SCC were relatively stable over time, the study had insufficient statistical power to detect predictors of marked improvements of deteriorations in SCC. It is possible that more variation could be detected in patients with more severe strokes and there may also be a need for SCC measures that are more sensitive to detect subtle SCC changes over time. In addition, with more than two repeated measures during follow-up, advanced statistical methods

will be useful to determine trajectories of change in physical post-stroke recovery, neuropsychological performance and SCC. Strengths of our study include the longitudinal design, the inclusion of a large sample size and the use of a validated instrument to explore SCC after stroke. Other unique aspects of this study are the simultaneous evaluation of demographic and clinical characteristics, OCP, psychological factors and ADL functioning in relation to the course and prediction of post-stroke SCC.

CONCLUSIONS

In conclusion, patients who report SCC at 3 months are likely to continue having these complaints at 1 year post-stroke. About half of the patients in this study remained stable and less than 10% displayed clinically significant changes in SCC in this time period. Having high levels of psychological distress at 3 months after stroke was an independent predictor for SCC at 12-months. The underlying cause of the perceived stress was not assessed in the current study, but psychological and behavioral interventions may target psychological distress in order to reduce cognitive complaints in post-stroke patients. Future intervention studies are needed to identify whether stroke-related psychological distress (e.g., troubles dealing with the physical, cognitive and or emotional consequences of stroke, experiencing important changes in life due to stroke) or other individual stress-related factors (e.g., having difficulties dealing with problems in life other than stroke) are optimal targets for improving SCC. Our results suggest that interventions aimed at reducing perceived stress (maybe by developing adequate coping skills) and depressive symptoms in the first few months after stroke might reduce sustained SCC and improve well-being during the first year following stroke.

REFERENCES

1] Pendlebury ST, Mariz J, Bull L, Mehta Z, Rothwell PM. MOCA, ACE-R, and MMSE versus the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network Vascular Cognitive Impairment Harmonization Standards Neuropsychological Battery after TIA and stroke. Stroke. 2012;43:464-469.

2] Lamb F, Anderson J, Saling M, Dewey H. Predictors of subjective cognitive complaint in post-acute older adult stroke patients. Arch Phys Med Rehabil. 2013;94:1747-1752.

3] van Rijsbergen MW, Mark RE, de Kort PL, Sitskoorn MM. Subjective cognitive complaints after stroke: A systematic review. J Stroke Cerebrovasc Dis. 2014;23:408-420.

4] Davis AM, Cockburn JM, Wade DT, Smith PT. A subjective memory assessment questionnaire for use with elderly people after stroke. Clin Rehabil. 1995;9:238-244.

5] Lincoln NB, Brinkmann N, Cunningham S, Dejaeger E, De Weerdt W, Jenni W, et al. Anxiety and depression after stroke: A 5 year follow-up. Disabil Rehabil. 2013;35:140-145.

6] Narasimhalu K, Wiryasaputra L, Sitoh YY, Kandiah N. Post-stroke subjective cognitive impairment is associated with acute lacunar infarcts in the basal ganglia. Eur J Neurol. 2013;20:547-551.

7] Van Heugten C, Rasquin S, Winkens I, Beusmans G, Verhey F. Checklist for cognitive and emotional consequences following stroke (CLCE-24): Development, usability and quality of the self-report version. Clin Neurol Neurosurg. 2007;109:257-262.

8] Xiong YY, Wong A, Mok VC, Tang WK, Lam WW, Kwok TC, et al. Frequency and predictors of proxy-confirmed post-stroke cognitive complaints in lacunar stroke patients without major depression. Int J Geriatr Psychiatry. 2011;26:1144–1151.

9] Maaijwee NA, Schaapsmeerders P, Rutten-Jacobs LC, Arntz RM, Schoonderwaldt HC, van Dijk EJ, et al. Subjective cognitive failures after stroke in young adults: Prevalent but not related to cognitive impairment. J Neurol. 2014;261:1300-1308.

10] Duits A, Munnecom T, van Heugten C, van Oostenbrugge RJ. Cognitive complaints in the early phase after stroke are not indicative of cognitive impairment. J Neurol Neurosurg Psychiatry. 2008;79:143-146.

11] Nijsse B, van Heugten CM, van Mierlo ML, Post MW, de Kort PL, Visser-Meily JM. Psychological factors are associated with subjective cognitive complaints 2 months post-stroke. Neuropsychol Rehabil. 2017;27:99-115.

12] van Rijsbergen MW, Mark RE, Kop WJ, de Kort PL, Sitskoorn MM. The role of objective cognitive dysfunction in subjective cognitive complaints after stroke. Eur J Neurol. 2017;24:475-482.

13] Liman TG, Heuschmann PU, Endres M, Floel A, Schwab S, Kolominsky-Rabas PL. Changes in cognitive function over 3 years after first-ever stroke and predictors of cognitive impairment and long-term cognitive stability: The Erlangen Stroke Project. Dement Geriatr Cogn Disord. 2011;31:291-299.

14] Brainin M, Tuomilehto J, Heiss WD, Bornstein NM, Bath PM, Teuschl Y, et al. Post-stroke cognitive decline: An update and perspectives for clinical research. Eur J Neurol. 2015;22:229-238.

15] Levine DA, Galecki AT, Langa KM, Unverzagt FW, Kabeto MU, Giordani B, et al. Trajectory of cognitive decline after incident stroke. Jama. 2015;314:41-51.

16] Rasquin SM, Welter J, van Heugten CM. Course of cognitive functioning during stroke rehabilitation. Neuropsychol Rehabil. 2013;23:811-823.

17] Tinson DJ, Lincoln NB. Subjective memory impairment after stroke. Int Disabil Stud. 1987;9:6-9.

18] van Rijsbergen MW, Mark RE, de Kort PL, Sitskoorn MM. The COMPlaints After Stroke (COMPAS) study: Protocol for a Dutch cohort study on poststroke subjective cognitive complaints. BMJ Open. 2013;3:e003599.

19] de Jonghe JF, Schmand B, Ooms ME, Ribbe MW. [Abbreviated form of the Informant Questionnaire on Cognitive Decline in the Elderly]. Tijdschr Gerontol Geriatr. 1997;28:224-229.

20] Brott T, Adams HP, Jr., Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: A clinical examination scale. Stroke. 1989;20:864-870.

21] van Rijsbergen MW, Mark RE, de Kort PL, Sitskoorn MM. Prevalence and profile of poststroke subjective cognitive complaints. J Stroke Cerebrovasc Dis. 2015;24:1823-1831.

22] Schmand B, Bakker D, Saan R, Louman J. [The Dutch adult reading test: A measure of premorbid intelligence]. Tijdschr Gerontol Geriatr. 1991;22:15-19.

23] Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand. 1983;67:361-370.

24] Sagen U, Vik TG, Moum T, Morland T, Finset A, Dammen T. Screening for anxiety and depression after stroke: Comparison of the Hospital Anxiety and Depression Scale and the Montgomery and Asberg Depression Rating Scale. J Psychosom Res. 2009;67:325-332.

25] Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med. 1997;27:363-370.

26] Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24:385-396.

27] Lee EH. Review of the psychometric evidence of the Perceived Stress Scale. Asian Nurs Res. 2012;6:121-127.

28] Michielsen HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: The Fatigue Assessment Scale. J Psychosom Res. 2003;54:345-352.

29] Mead G, Lynch J, Greig C,Young A, Lewis S, Sharpe M. Evaluation of fatigue scales in stroke patients. Stroke. 2007;38:2090-2095.

30] Sanderman R, Arrindell WA, Ranchor A, Eysenck HJ, Eysenck SBG. [Measurement of personality traits using the Eysenck Personality Questionnaire: A manual]. Groningen: Noordelijk Centrum voor Gezondheidsvraagstukken, Rijksuniversiteit Groningen; 1995.

31] Sato T. The Eysenck Personality Questionnaire brief version: Factor structure and reliability. J Psychol. 2005;139:545-552.

32] Sanderman R, Ormel J. [The Utrecht Coping List (UCL): Validity and reliability]. Gedrag Gezond. 1992;20:32-37.

33] Schreurs PJG, Van de Willege G, Brosschot JF, Tellegen B, Graus GMH. [The Utrechtse Coping List: UCL manual]. Utrecht: Swets en Zeitlinger; 1993.

34] van den Akker M, Buntinx F, Metsemakers JF, Knottnerus JA. Marginal impact of psychosocial factors on multimorbidity: Results of an explorative nested case-control study. Soc Sci Med. 2000;50:1679-1693.

35] Warttig SL, Forshaw MJ, South J, White AK. New, normative, English-sample data for the short form Perceived Stress Scale (PSS-4). J Health Psychol. 2013;18:1617-1628.

36] Holbrook M, Skilbeck CE. An activities index for use with stroke patients. Age Ageing. 1983;12:166-170.

37] Post MW, de Witte LP. Good inter-rater reliability of the Frenchay Activities Index in stroke patients. Clin Rehabil. 2003;17:548-552.

38] Schuling J, de Haan R, Limburg M, Groenier KH. The Frenchay Activities Index. Assessment of functional status in stroke patients. Stroke. 1993;24:1173-1177.

39] Jacobson NS, Truax P. Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. J Consult Clin Psychol. 1991;59:12-19.

CHAPTER 7
APPENDIX

Table A1. Differences at baseline between participants lost to follow-up and those included

	Drop-out N = 53	Inclusion N = 155	p-value
Age in years, mean ± SD	67.7 ± 13.3	64.0 ± 11.9	.06
Males, n (%)	29 (54.7%)	108 (69.7%)	**.05**
D-NART, IQ-estimation, mean ± SD (N = 150)	93.7 ± 15.2	96.0 ± 11.9	.26
Ischemic stroke, n (%)	51 (96.2%)	146 (94.2%)	.73
Stroke side			.20
Left, n (%)	15 (40.6%)	63 (40.6%)	
Right, n (%)	32 (60.4%)	72 (46.5%)	
Not differentiated, n (%)	6 (11.3%)	20 (12.9%)	
NIHSS, stroke severity at admission, median [Q1 – Q3]	3 [2 – 5]	3 [2 – 5]	.59
CLCE-c	3.5 ± 2.8	3.3 ± 2.4	.68
CLCE-w	2.2 ± 2.4	1.9 ± 2.2	.56
CLCE-t	9.0 ± 7.6	8.5 ± 6.6	.66
OCI- index	7.0 ± 4.0	5.6 ± 3.5	**.03**
HADS-depression	5.8 ± 3.9	4.9 ± 3.7	.20
HADS-anxiety	5.2 ± 4.1	4.6 ± 3.8	.37
PSS-4, perceived stress	5.4 ± 2.7	4.9 ± 2.7	.35
FAS, fatigue	25.3 ± 7.2	24.6 ± 6.7	.54
EPQ-RSS, neuroticism	3.6 ± 3.2	3.4 ± 2.9	.61
EPQ-RSS, extraversion	6.7 ± 3.1	6.7 ± 3.2	.94
UCL-avoidance	6.7 ± 1.6	6.0 ± 1.7	**.02**
UCL-active handling	13.3 ± 3.0	13.7 ± 2.9	.44
UCL-seeking social support	11.4 ± 2.8	10.4 ± 2.6	**.04**
UCL-palliative reaction	4.6 ± 1.6	4.3 ± 1.2	.29
FAI, instrumental ADL	22.4 ± 7.0	22.7 ± 8.1	.85

Abbreviations: *ADL, activities of daily living; CLCE, Checklist for Cognitive and Emotional consequences following stroke, content, worry, total score; D-NART, Dutch version of the National Adult Reading Test; EPQ-RSS, Eysenck Personality Questionnaire Revised Short Scale; FAI, Frenchay Activities Index; FAS, Fatigue Assessment Scale; HADS, Hospital Anxiety and Depression Scale; IQ, intelligence quotient; NIHSS, National Institutes of Health Stroke Scale; OCI, objective cognitive impairment; PSS-4, Perceived Stress Scale-short form; UCL, Utrecht Coping List.*

Table A2. *Multiple regression between 3-months characteristics and 12-months subjective cognitive complaints (CLCE-w and CLCE-cognitive total)*

	CLCE-w						CLCE-t					
	Correlations		Multiple Regression				Correlations		Multiple Regression			
			Model 1		Model 2				Model 1		Model 2	
	Pearson's r	p-value	β	p-value	β	p-value	Pearson's r	p-value	β	p-value	β	p-value
Block 1												
CLCE, baseline score	0.65	**<.001**	Not entered		0.57	**<.001**	0.68	**<.001**	Not entered		0.56	**<.001**
Block 2												
Age	-0.06	.45	-0.04	.59	-0.02	.73	-0.07	.36	-0.06	.43	-0.06	.37
Sex (male)	-0.05	.55	-0.03	.69	0.02	.77	-0.08	.34	-0.04	.65	0.002	.97
D-NART, IQ-estimation	-0.10	.20	0.13	.21	0.02	.86	-0.14	.09	0.09	.35	-0.01	.87
NIHSS, stroke severity	0.02	.82	-0.02	.77	0.04	.55	-0.01	.95	-0.03	.68	0.01	.94
Block 3												
OCI-index	0.17	**.04**	0.20	**.04**	0.04	.69	0.20	**.02**	0.20	**.04**	0.06	.51
Block 4												
HADS-depression	0.41	**<.001**	†		0.23	**.003**	0.39	**<.001**	†		†	
HADS-anxiety	0.37	**<.001**	†		†		0.37	**<.001**	†		†	
PSS4, perceived stress	0.47	**<.001**	0.30	**.004**	†		0.50	**<.001**	0.26	**.01**	0.22	**.004**
FAS, fatigue	0.35	**<.001**	†		†		0.39	**<.001**	0.15	.10	†	
Block 5												
EPQ-RSS, neuroticism	0.46	**<.001**	0.28	**.01**	†		0.48	**<.001**	0.27	**.01**	†	
EPQ-RSS, extraversion	-0.11	.22	†		†		-0.10	.22	†		†	
UCL-avoidance	0.24	**.004**	†		†		0.28	**.001**	†		†	
UCL-active handling	-0.18	**.03**	†		†		-0.22	**.01**	†		†	
UCL-seeking social support	0.09	.29	†		†		0.07	.43	†		†	
UCL-palliative reaction	0.16	.05	†		†		0.19	**.03**	†		†	

Table A2. *Continued*

	CLCE-w						CLCE-t					
	Correlations		Multiple Regression				Correlations		Multiple Regression			
			Model 1		Model 2				Model 1		Model 2	
	Pearson's r	p-value	β	p-value	β	p-value	Pearson's r	p-value	β	p-value	β	p-value
Block 6												
FAI, instrumental ADL	-0.15	.06	†		†		-0.19	.02	†		†	

Model 1: *CLCE baseline score (at 3 months) not included.* ***Model 2:*** *CLCE baseline score included. Variables in block 1 - 3 were entered using the enter procedure. In block 4-6, a forward procedure was used.* ***Sign:*** *† Variables that were removed from the analysis using a forward procedure.* ***Abbreviations:*** *ADL, activities of daily living; CLCE, Checklist for Cognitive and Emotional consequences following stroke, content, worry, total score; D-NART, Dutch version of the National Adult Reading Test; EPQ-RSS, Eysenck Personality Questionnaire Revised Short Scale; FAI, Frenchay Activities Index; FAS, Fatigue Assessment Scale; HADS, Hospital Anxiety and Depression Scale; IQ, intelligence quotient; NIHSS, National Institutes of Health Stroke Scale; OCI, objective cognitive impairment; PSS-4, Perceived Stress Scale-short form; UCL, Utrecht Coping List.*

Table A3. *Multiple regression between 3-months characteristics and 12-months objective cognitive functioning*

	Model 1		Model 2	
	Standardized β	p-value	Standardized β	p-value
Block 1				
OCI-index	Not entered		0.73	**<.001**
Block 2				
CLCE-c	0.12	.08	0.07	.21
Block 3				
Age	0.06	.41	0.16	**.004**
Sex (male)	0.04	.60	0.04	.41
D-NART, IQ-estimation	-0.45	**<.001**	-0.11	.10
NIHSS, stroke severity	0.13	.08	0.03	.53
Block 4				
HADS-depression	†		†	
HADS-anxiety	†		†	
PSS4, perceived stress	†		†	
FAS, fatigue	†		†	
Block 5				
EPQ-RSS, neuroticism	†		†	
EPQ-RSS, extraversion	†		†	
UCL-avoidance	†		†	
UCL-active handling	†		†	
UCL-seeking social support	†		†	
UCL-palliative reaction	†		†	
Block 6				
FAI, instrumental ADL	-0.28	**<.001**	†	

Model 1: *baseline score (at 3 months) of OCI-index not included.* ***Model 2:*** *baseline score of OCI-index included. Variables in block 1 - 3 were entered using the enter procedure. In block 4-6, a forward procedure was used.* ***Signs:*** *† Variables that were removed from the analysis using a forward procedure.* ***Abbreviations:*** *ADL, activities of daily living; CLCE, Checklist for Cognitive and Emotional consequences following stroke, content; D-NART, Dutch version of the National Adult Reading Test; EPQ-RSS, Eysenck Personality Questionnaire Revised Short Scale; FAI, Frenchay Activities Index; FAS, Fatigue Assessment Scale; HADS, Hospital Anxiety and Depression Scale; IQ, intelligence quotient; NIHSS, National Institutes of Health Stroke Scale; OCI, objective cognitive impairment; PSS-4, Perceived Stress Scale-short form; UCL, Utrecht Coping List.*

CHAPTER 8
GENERAL DISCUSSION

GENERAL DISCUSSION

The aim of the research presented in this dissertation was to explore the prevalence, determinants and course of subjective cognitive complaints (SCC) among adult stroke patients during the first 12 months after hospitalization for stroke. The studies described in the previous chapters are based on the COMPlaints After Stroke (COMPAS) study, a prospective cohort study of stroke patients, performed between 2009 and 2014. This chapter describes: (1) a summary of the main findings, (2) methodological considerations, and (3) clinical implications and suggestions for future research.

1. Overview of the main findings

The annual incidence of stroke is approximately 41,000 in The Netherlands [1]. Stroke is often followed by impairments in physical, cognitive and/or psychological domains, thereby negatively affecting activities of daily living (ADL) and quality of life (QoL) [2-6]. These consequences of stroke often increase patients' dependency on the health care system as well as their social support network and may lead to substantial psychological, social and economic burden [7-10]. Post-stroke cognitive impairment is one of the stroke sequelae with an impact on participation in rehabilitation programs and adherence to secondary prevention treatments. Although numerous studies have explored post-stroke cognitive performance objectively, by using neuropsychological tests covering one or more cognitive domains (see for example the literature reviews performed by Brainin et al. [11], Moran et al. [12], Makin et al. [13], Edwards et al. [14], Cumming et al. [15] and De Haan et al. [16]), less scientific attention has been paid to SCC after stroke, i.e., what cognitive difficulties people report themselves.

Chapter 2 [17] describes the results of a systematic review on SCC among stroke survivors. Despite the heterogeneity of the 26 studies included with respect to sample characteristics, the time interval between the stroke event and assessment of SCC, and the instruments used to evaluate SCC, all found SCC to be common after stroke. A main problem of the studies evaluated was that there was no consensus (gold standard) on how to define SCC. Based on the literature, the following definition of SCC was proposed (see Chapter 2 [17]): The cognitive difficulties or problems reported by patients themselves, consisting of two components, i.e., *content* (SCC-c, covering the nature/domain of SCC, e.g., memory- or concentration-related SCC) and *worry* (SCC-w, indicating the impact of SCC in terms of interference in daily life, annoyance, and/or worry). This definition was used throughout the remaining chapters in this dissertation. Other findings of the literature review were that the associations of demographic and clinical characteristics, objective cognitive performance (OCP) and depression with SCC were inconsistent and that SCC tended to increase over time.

The literature search for the systematic review was last updated in April 2013. Two relevant studies on post-stroke SCC have been published since then and are

briefly summarized here. In 2014, Maaijwee et al. [18] found that subjective memory and executive failures (an indication of SCC-c, measured with a semi-structured interview) were prevalent and more common among young (aged ≤ 50 years) stroke and transient ischemic attack patients in the chronic phase (mean 11.0 ± 8.2 years post-stroke), than among a non-stroke comparison group (matched on age and sex to the patient sample). Although a weak, but significant, association was found between OCP and SCC on the memory domain, the prevalence of SCC did not differ between patients with versus those without objective cognitive impairment (OCI). Only severity of fatigue was independently associated with the presence of SCC [18]. In 2015, Nijsse et al. [19] found SCC-c to be prevalent in the early phase after stroke; 68.4% reported at least one SCC-c at 2 months post-stroke. From the demographic, clinical and psychological factors evaluated, only proactive coping style was independently associated with SCC, with more proactive coping being related to less SCC [19]. These finding are consistent with those reported in the systematic review as presented in Chapter 2 [17].

Chapter 3 [20] presents the rationale and design of the COMPAS study. It is the first prospective cohort study on post-stroke SCC and includes comprehensive assessments of subjective (e.g., self-reported depression, anxiety, perceived stress, fatigue) and objective variables (e.g., demographic and clinical characteristics, and neuropsychological tests for OCP). The primary outcome variable in this dissertation is post-stroke SCC, assessed using the Cognitive Failures Questionnaire (CFQ) [21, 22] and the interview-based Checklist for Cognitive and Emotional consequences following stroke (CLCE) [23] inventory. A total of 211 post-stroke patients and a comparison group of 155 individuals were recruited in this project.

In **Chapter 4** [24], the prevalence and profile of SCC of patients at 3 months after their stroke are compared to those from a non-stroke comparison sample. Two instruments were used to evaluate SCC, including the CFQ [21, 22] (a generic tool) and the CLCE [23] (a stroke-specific instrument). In line with the literature on post-stroke SCC (Chapter 2 [17]), these complaints were highly prevalent among stroke survivors: 89.2% reported one or more SCC-c, 66.9% reported one or more SCC-w (measured with the CLCE), compared to respectively 65.2% and 40.7% of the non-stroke sample. The stroke-profile typically included SCC related to memory, attention and concentration, executive functioning and language. Whether and how the prevalence and profile of SCC-c and SCC-w differed between those with versus those without a stroke, depended on the SCC instrument used. Patients tended to report less SCC-c and similar levels of SCC-w compared to the non-stroke participants on the CFQ, while on the CLCE, SCC-c related to memory, attention/concentration, executive functioning and language, and SCC-w related to attention, were more prevalent among the stroke survivors. The results on the CLCE are consistent with the literature on post-stroke SCC and as the focus in this dissertation is on the stroke population, the CLCE interview was chosen to be the most appropriate measure of SCC in Chapters 5 through 7.

Chapter 5 [25] presents the association between OCP and SCC at 3 months after stroke. Both conventional neuropsychological OCP tests (e.g., the Stroop Color Word Test [26]) and ecologically valid tests that closely resemble daily life cognitive activities (e.g., the Rivermead Behavioral Memory Test, RBMT [27]) were included. The strongest OCP-SCC associations were observed when ecologically valid tests in the memory domain (i.e., the RBMT) were used (β = -0.34, p = .001 for SCC-c and β = -0.31, p = .002 for SCC-w). An OCI-index was calculated which provided a measure of total OCP dysfunction (the total number of neuropsychological tests on which the patient showed impaired performance compared to established norms). The OCI-index was significantly associated with SCC-c (β = 0.25, p = .01) and SCC-w (β = 0.31, p = .001) after adjusting for the effects of age, sex and IQ-estimation. Specifically, the number of SCC on the CLCE increased markedly when patients performed poorly (i.e., below the published norm-based cut-off value) on more than 8 neuropsychological tests. There was no significant association between stroke severity or stroke location with SCC. When cognitive domains were investigated separately, results for SCC-c differed slightly from those obtained for SCC-w. Whereas for SCC-c, significant associations were found between OCP and SCC on the domains of memory, executive functioning and expressive language, for SCC-w, significant OCP-SCC associations were obtained in the domains memory, mental speed/attention and executive functioning. The OCP-SCC associations are significant but cannot fully explain the high prevalence of SCC among stroke survivors. Other factors are therefore likely to also contribute to post-stroke SCC.

Chapter 6 explores the extent to which depression, anxiety, perceived stress and fatigue are related to SCC at 3 months after stroke. These psychological variables were all significantly correlated with SCC and the effect sizes of these associations were of moderate magnitude (Pearson's r values ranging from 0.38 to 0.45; p-values all < .001; β = 0.35 – 0.39, all p-values < .001 when adjusted for age, sex, IQ, stroke severity, OCI and ADL). These psychological constructs could reflect a general measure of psychological distress [28]. The role of (underlying) personality factors and coping styles was also examined. After including personality traits and coping style into the model, independent relations for SCC-c were found with fatigue (β = 0.26, p = .003), neuroticism (β = 0.21, p = .05) and OCI (β = 0.20, p = .03), and for SCC-w with anxiety (β = 0.27, p = .01), perceived stress (β = 0.25, p = .01) and OCI (β = 0.33, p = .001). Whereas the relationship between depression, anxiety and perceived stress with SCC was attenuated when neuroticism was included, the relationship between fatigue and SCC was independent of neuroticism. These findings indicate that fatigue and psychological distress play a role in SCC and that personality factors, particularly neuroticism, may be a critical factor in the association between psychological distress with SCC after stroke.

The cross-sectional designs presented in the previous chapters are typical for the current state-of-the-art in the literature examining post-stroke SCC. These designs do not enable causal inference and provide no information about the longitudinal changes in SCC.

Chapter 7 documents SCC at 3 and 12 months following stroke and describes the predictive value of demographic and clinical patient characteristics, OCP and psychological factors at 3 months after stroke for subsequent SCC, measured using the CLCE, at 1-year follow-up. Results showed that SCC remained stable from 3 to 12 months after stroke (the mean CLCE scores at follow-up were almost identical to those seen at baseline; 3 versus 12 months CLCE-c = 3.3 ± 2.4 versus 3.3 ± 2.6, $p > .99$; CLCE-w = 1.9 ± 2.2 versus 2.1 ± 2.5, $p = .28$). Furthermore, at the individual patient level, more than half of the patients (CLCE-c, 56.8%; CLCE-w ,64.5%) had a stable CLCE score (change < 1 standard deviation, equivalent to 0 - 1 points). Analyses using the reliable change index also confirmed the stability of SCC from 3 to 12 months post-stroke: fewer than 10% of the patients displayed clinically significant changes over time (8 patients worsened and 3 improved). The presence of SCC at follow-up was therefore primarily predicted by baseline SCC (CLCE-c: $\beta = 0.54$, $p < .001$; CLCE-w: $\beta = 0.57$, $p < .001$). In addition to baseline SCC at 3 months post stroke, an additional independent predictive value was found for perceived stress ($\beta = 0.23$, $p = .003$, for CLCE-c) and depression ($\beta = 0.23$, $p = .003$, for CLCE-w), whereas demographic and clinical characteristics and OCP at 3 months after stroke did not independently predict SCC at 1 year follow-up.

2. Methodological considerations

The findings of the studies described in this dissertation need to be considered in the context of the methodological merits and limitations of this project. In the following sections, a discussion is provided regarding general and design-related methodological issues, study sample characteristics, and the terminology and measurement of SCC in stroke survivors.

2.1. Design-related considerations

In Chapters 4 through 6, cross-sectional data were used, which meant that no conclusions could be drawn regarding causality. In Chapter 4 [24] it was assumed that stroke is the reason for SCC to be more common among the patients than among the non-stroke comparison group. Prospective data that include pre-stroke evaluations of SCC and comprehensive neuropsychological assessments are practically not feasible because a stroke usually occurs unexpectedly. Furthermore, as described in Chapters 5 [25] and 6, post-stroke SCC was found to be associated with OCP, measures of psychological distress, fatigue and neuroticism, independent of demographics, clinical characteristics and coping style. The hypothesis of this dissertation was that SCC is a consequence of OCP and psychological distress, something which is supported by the results of the longitudinal study presented in Chapter 7. Perceived stress and depressive symptoms 3 months after stroke independently predicted SCC at 12 months. However, the 'reversed pathway' is also possible, in other words, that SCC negatively affect cognitive functioning [29] or leads to psychological distress. For OCP however, no evidence was found for such a pathway because SCC at 3 months did not independently predict OCP at 1 year follow-up. The effect of SCC on future psychological well-being has yet to be determined.

The longitudinal study presented in this dissertation examined data collected at two time points, namely at 3 and 12 months after stroke. The COMPAS study also included an additional telephone-based evaluation at 6 months post-stroke. These data were not included in the current project for methodological reasons as different procedures (telephone at 6 months versus face-to-face interview at 3 and 12 months follow-up) were used to assess SCC. Also, future studies are needed to investigate the data collected at 24 months.

The study may have been underpowered to detect small effect sizes. The target of the COMPAS study was to include at least 300 patients to statistically analyze small effect sizes and employ multivariate statistical models. As described in Chapters 4 through 7, 211 patients with stroke were included, of whom 208 had an SCC assessment at 3 months. Despite this lower than targeted number, this is still one of the larger studies on post-stroke SCC (McKevitt et al. [30] have the largest sample size so far, with 1251 participants) and several significant cross-sectional and longitudinal predictors of post-stroke SCC have been identified (Chapters 4 through 7).

It is possible that not all variables relevant to SCC were assessed in the COMPAS study. Stroke location was defined broadly as being either left-sided, right-sided or not differentiated. This classification is relatively global and may explain why no associations were found between stroke location and post-stroke SCC in this dissertation. The Oxford Community Stroke Project classification system [31], giving more information on size and site of the stroke, was also determined as part of the COMPAS study (data not shown). The sample sizes of the individual categories were however too small to enable adequate statistical analyses on the associations between stroke localization and post-stroke SCC. Liebermann et al. [32] and Narasimhalu et al. [33] found an association between SCC and lesions in the anterior thalamus and basal ganglia, respectively. Such specific information on stroke location was not gathered in the COMPAS study. Future studies with larger samples are needed to investigate relations between lesion-specific stroke characteristics and SCC.

Meta-cognition (i.e., cognitions about cognition [34]) is another potentially relevant variable in relation to post-stroke SCC, but was not included in the present project. Meta-cognition consists of three factors, including: knowledge about cognitive functions, monitoring of the cognitive system, and beliefs about cognition [35]. Memory self-efficacy (one of the aspects of meta-cognition and referring to the feeling of control and mastery of one's memory [35, 36]), has been related to both OCP and SCC in studies investigating elderly participants [37-39]. This topic has also received attention in the stroke literature. Aben et al. [36] found memory self-efficacy to be a predictor of memory-related SCC, independent of age and depression. The meta-cognition perspective might also be applicable to other cognitive domains than memory, e.g., attention and concentration and executive functioning. As

shown in Chapter 4 [24], we found evidence for stroke to be associated with these domains of OCP and additional research is needed to clarify the role of meta-cognition in the association between OCP and SCC in stroke survivors.

2.2. Potential issues related to study sample characteristics

The sample evaluated in this project had relatively mild stroke severity (median National institutes of Health Stroke Scale [40] score 3 out of 42), which may explain why no associations were found between the severity of stroke and SCC. Additionally, the majority of patients (85.8%) were considered to be recovered well enough to be discharged home after their hospitalization for stroke. At 3 months post-stroke, most patients were able to function independently in basic ADL (Barthel Index [41, 42] = 19.6 ± 1.0; 90% had ≥ 19 points, with 20 being the maximum score). Although severity of stroke was not a selection criterion, the burden of the assessments (2 to 2.5 hours at 3, 12 and 24 months) may have resulted in non-eligibility or non-participation of patients with more severe impairments after stroke. In addition, patients with severe aphasia were excluded as they were not able to participate. The results of this study can therefore not be unequivocally generalized to patients who have suffered a more severe stroke or to those with severe communication disorders. However, the present sample potentially reflects exactly that part of the stroke population which is most likely to report SCC. Patients who are living at home after their stroke and who are trying to resume their pre-stroke daily life activities are probably more often confronted with the practical consequences of SCC-related difficulties than those living in a rehabilitation setting or a nursing home [29, 43, 44].

An additional limitation lies in the characteristics of the non-stroke comparison sample (analyzed in Chapter 4 [24]). Participants in this group differed significantly from the stroke patients in that they were more likely to be younger, female, and more highly educated and/or had a higher IQ. Comparisons between the stroke and the non-stroke sample in Chapter 4 [24] were therefore made with matching the groups on these aspects. The disadvantage of these types of matching procedures is that only a subset of the participants evaluated could be included in the analyses. In addition, matching of cases and controls creates several statistical problems, including dependency of the data, requiring conditional statistical models. Future large-scale epidemiological studies using case-cohort designs may be helpful in addressing the issue of matching. Nonetheless, because the primary focus of the present project was on post-stroke SCC, results for the non-stroke sample were included in Chapter 4 [24] only and Chapters 5 through 7 focused on the patients with stroke.

2.3. Definitional issues related to subjective cognitive complaints

As mentioned in Chapter 1 and 2 [17], there is no 'gold standard' definition of SCC in the literature to date. Whereas some studies focused exclusively on SCC that interfered with daily life [36, 43, 45], others evaluated the presence of cognitive difficulties irrespective of their impact [30, 33, 44, 46-48]. Experiencing difficulties or problems in daily cognitive tasks, however, is not necessarily burdensome, annoying, irritating, or a reason for concern. Patients who have adequate coping strategies to compensate for their deficits may report less or no SCC-related impact on their daily life activities [36]. Tinson and Lincoln [49] already suggested in 1987 that memory-related SCC after stroke are determined both by lifestyle and cognitive ability. This may apply to SCC in general. The aforementioned issues related to meta-cognition may be of particular relevance in distinguishing between the presence versus impact of SCC. In this dissertation, the term '*content*' was used to describe the nature and severity of SCC (i.e., the presence or absence of memory, concentration, language or executive functioning problems). SCC from this 'content' dimension were explored, irrespective of whether the complaint interfered with daily life. The term *'worry'* was used specifically describe only SCC which had a self-reported impact (or concern) on the person's daily life functioning. The 'worry' dimension of SCC is therefore logically dependent on the 'content' dimension, as the former can only occur if the latter is present. We therefore used the 'content' dimension of SCC as the primary focus of this project. Future studies are needed to disentangle the importance of the nature and type of SCC from the impact and patient-reported concerns and worries related to these SCC. The present study shows that the content component is a useful index of post-stroke SCC, particularly when it is assessed using interview-based assessment tools such as the CLCE (see Chapter 4 [24]).

In addition to the two dimensions of SCC, there are also potential methodological issues regarding the assessment of SCC. The CFQ and CLCE are commonly used instruments in the evaluation of SCC [21, 29, 43, 50-68]. The CFQ is as a generic self-report questionnaire tool whereas the CLCE is a stroke-specific instrument designed to assess SCC in patients surviving a stroke or other central nervous system injury. As described in Chapter 4 [24], the CLCE was more sensitive for SCC assessed at 3 months than the CFQ. The CFQ is a paper-pencil questionnaire that is filled out by the participant and consists of long sentences that need to be answered on a 5-point Likert scale. It is possible that for some patients, the CFQ might be too difficult to be reliably filled out at 3 months post-stroke. The CLCE items, on the other hand, are interview-based short questions that need to be answered with yes/no. The CLCE results may therefore be biased by the interviewer's knowledge of the patients' 'stroke status', thereby inflating the differential properties of the CLCE versus the CFQ. This methodological difference between the CFQ and the CLCE may partly explain the observed differences in identifying SCC in post-stroke patients as outlined in Chapter 4 [24].

The stability in SCC over time, described in Chapter 7, may partially result from the design characteristics of the CLCE. Specifically, the response categories of the CLCE interview are scored as either 'SCC not present', 'presence uncertain', 'present, but no impact on daily life', or 'present and negatively affecting daily life.'

This response format may not be particularly sensitive to subtle changes in the prevalence or impact of SCC. Although SCC may subjectively change over time in terms of being less frequent and/or as having less impact than at baseline, the CLCE scores may be approximately the same at both assessment time points. The Likert scale scoring system of the CFQ, ranging from 0 (never) to 4 (very often) may be more appropriate to map subjective change in SCC. However, explorative analyses of change in the CFQ does not support this suggestion (CFQ at 3 versus 12 months = 29.5 ± 14.3 versus 29.7 ± 12.7, p = .87). The stability in SCC from 3 to 12 months post-stroke may be the result of the specific stroke sample evaluated as most strokes were relatively mild, characteristics of the SCC assessment tools (e.g., sensitivity to change), potential floor effects as most patients had mild to moderate SCC, personality characteristics related to SCC (neuroticism in particular) which also tend to be stable over time, or a real phenomenon of stabilizing complaints that remain constant after 3 months post-stroke.

A general problem with self-assessments in patients with neurological conditions is that disease-related deficits may bias self-reports [32, 47, 48, 69, 70]. At least four factors have been suggested in the literature that may influence the number and severity of post-stroke SCC: (1) patients have to remember their pre- and post-stroke cognitive functioning and need to be able to compare their current cognitive abilities with their pre-stroke abilities; (2) the consequences of stroke may be denied or there is indifference to deficits as a result of a stroke-related reactive psychological response; (3) unawareness of problems directly caused by brain damage (anosognosia) may result in attenuated SCC reports; and (4) depressive mood of both the patient and the spouse may increase the number and severity of SCC [32, 47, 48, 69]. To overcome these problems, some researchers used proxy-reports to evaluate patients' SCC [71], but this also raises interpretational problems. Caregiver burden among spouses of stroke patients has been linked to higher rates of depression, anxiety, cardiovascular disease, general ill-health, mortality and a poor quality of life [10], which may indirectly affect the reliability of reports on patients' SCC [32, 69, 72]. The data of the present project indicate that stroke-related deficits per se do not account for the high prevalence of SCC in these patients. None of the clinical characteristics was significantly associated with SCC. In this dissertation, the primary contributing factor associated with post-stroke SCC was psychological distress, particularly anxiety and perceived stress (with the underlying factor potentially being neuroticism) and fatigue. These results suggest that it is not the stroke severity, but rather the psychological reaction to the stroke that drives SCC. This perspective opens several lines of clinical interventions (see below; Clinical Implications).

2.4. Miscellaneous methodological considerations

The neuropsychological measures of OCP in this project are all frequently used instruments in both research and clinical practice. The allocation of individual tests to specific cognitive domains was based on the literature and clinical experience [73, 74]. However, the classification of neuropsychological tests in specific domains of cognitive functioning is not always clear-cut; there are no 'pure' tests which only measure one domain [73]. Tests almost always assess multiple cognitive domains. For example, tests assessing executive functioning also include other cognitive domains such as attention and memory. The categorization used in Chapters 3 [20] and 5 [25] may have influenced the presence and/or magnitude of the associations found between OCP and SCC. Therefore, an overall OCI-index was computed in addition to domain-specific analyses. The results indicate that such an overall index may be important in identifying patients with high SCC.

The Hospital Anxiety and Depression Scale (HADS) [75] was used to assess the severity of depressive symptoms and anxiety. The instrument is a screening test and as such, it does not provide a clinical diagnosis of a depressive or anxiety disorder. Although the instrument is frequently used after stroke, both in research and in clinical practice, other instruments have also proven useful as screening tools for mood and anxiety disorders after stroke (e.g., the 9-item Patient Health Questionnaire, PHQ-9 [76], for detecting major depression [77]). A recent systematic review indicates that the HADS is an accurate assessment tool for the identification of post-stroke anxiety [77], but the Generalized Anxiety Disorder 7-item scale (GAD-7 [78]) is increasingly used to identify individuals with anxiety disorders [79]. A recent study showed that combining the PHQ-9 and GAD-7 may be efficient in a variety of medical settings [80]. Some evidence suggests that the HADS may be an index of general psychological distress [81-83], rather than a disorder-specific assessment tool. This perspective is consistent with the approach outlined in Chapter 6, in which anxiety and depression, as well as perceived stress and fatigue, were construed as indicators of psychological distress in multivariable models. The longitudinal analyses presented in Chapter 7 indicated that perceived stress 3 months after stroke is an independent predictor of SCC at 12 months post-stroke and that depressive symptoms at 3 months post-stroke predict subsequent impact of SCC at 12 months follow-up.

Coping styles may also be an important factor in post-stroke SCC [54]. The 15-item Utrecht Coping List [84, 85] was used to measure four aspects of coping style, including avoidance, active handling, seeking social support and a palliative reaction style. Data presented in Chapter 6 indicate that avoidance and (low) active coping styles are linked to post-stroke SCC in unadjusted analyses, but that these associations were attenuated in multivariate models. These coping strategies are classified as 'reactive coping styles', i.e., ways of dealing with problems in response to a stressor from the past or present [86, 87]. Another category comprises the proactive coping styles, meaning the strategies people use to detect and anticipate on potential stressors to prevent them from occurring or to reduce their impact [88]. Nijsse et al. [54] found proactive coping styles to be independently associated with post-stroke SCC. The present study did not find support for this association, but a direct assessment of proactive coping strategies was not obtained in the COMPAS study.

It is possible that coping styles that used to be effective in patients' pre-stroke daily life situations are no longer effective after stroke. Potentially maladaptive coping styles may adversely affect SCC as well as psychological adjustments to stroke. Observational and clinical studies are needed to disentangle the role of post-stroke reactive psychological conditions (e.g., depression) from personality factors and coping styles in order to develop adequate psychological interventions in patients who survive a stroke.

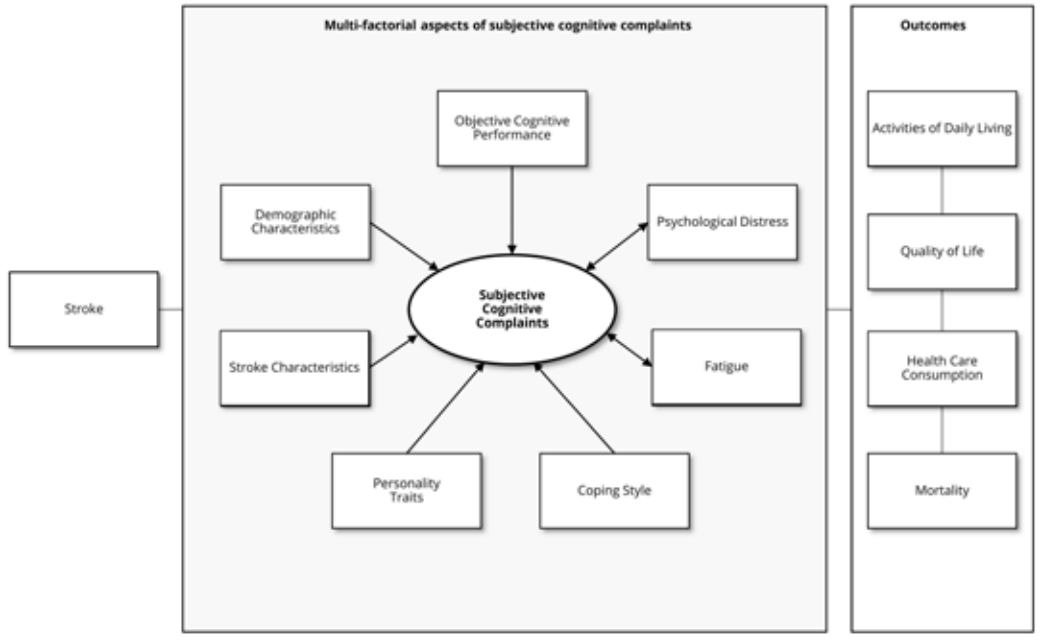
Despite these methodological considerations and limitations of the studies presented in this dissertation, the longitudinal COMPAS study is unique in evaluating SCC in stroke survivors, while taking a wide range of subjective and objective variables into account. A relatively large sample of patients was included and the prevalence and nature of post-stroke SCC was compared to a non-stroke comparison group. Validated instruments were used and participants were followed-up systematically. This dissertation describes the results of the first studies based on the COMPAS project and expands the scientific knowledge of SCC after stroke.

3. Clinical implications and future directions

The results presented in this dissertation provide evidence for the high prevalence of SCC among stroke survivors at 3 months after stroke (estimates > 89%; Chapters 4 through 6 [24, 25]), which tend to persist during the first year after hospitalization (SCC prevalence > 80%; Chapter 7). This highlights the importance of clinicians being alert to the presence of such complaints in the first few months after stroke. Screening for SCC during the scheduled clinical follow-up moments might be helpful, preferably using a stroke-specific SCC interview (Chapter 4 [24]). It should be noted that, although patients may experience deficits in daily life cognitive tasks, they probably will not complain about them when they are able to compensate for these problems [36]. A differentiation between SCC with and without impact on daily life functioning may be useful. Specifically, asking whether patients need help for their SCC is relevant, both in future research and in clinical practice. Also, reporting no SCC might not always be congruent with reality and/or the opinion of relatives or significant others. Unawareness, coping style, denial, cognitive impairment and other factors may determine whether or not patients report SCC. If the focus is on the patient-perspective and he/she reports not to suffer from cognitive difficulties, an intervention for the patient might not be necessary. Helping proxies on how to deal with the factors causing the non-report of SCC might be more appropriate instead. It is possible that denial of SCC is a clinical challenge in post-stroke patients whereas amplification of SCC may be a challenge in patients seeking health care in the absence of stroke or other well-identified neurological diseases; additional research is needed to establish whether this general perspective is correct. It will be important to expand the results on SCC after stroke to different neurological patient groups (e.g., patients with multiple sclerosis, a brain tumor, or Parkinson's disease), which may broaden the theoretical and clinical implications of the present findings.

Multiple factors may contribute to SCC after hospitalization for stroke (see Figure 1). Objective cognitive impairment is likely to play a role in addition to multiple psychological factors. Neuropsychological assessment may be used to explore whether SCC can be linked to cognitive impairment. The results presented in Chapter 5 [25] suggest that when SCC are present, ecologically valid tests are relevant to use in addition to the more conventional instruments. Direct links between OCP and SCC are most likely to be found on the memory domain when using tests with high ecological validity (e.g., the Rivermead Behavioral Memory Test). Future research might evaluate whether the OCP-SCC link on other cognitive domains is improved when more ecologically valid instruments are used (e.g., the Test of Everyday Attention [89], the complete Behavioral Assessment of the Dysexecutive Syndrome battery [90], the Cambridge Prospective Memory Test [91]). Data presented in this dissertation additionally indicate that there may be a threshold of cumulative objective cognitive deficits above which patients experience markedly elevated SCC.

Figure 1. *Conceptual model of the variables associated with SCC after stroke*



Note: *The model describes the categories of the variables found to be associated with post-stroke SCC in the literature and/or in this dissertation, including: background variables (demographic characteristics), clinical variables (stroke characteristics), personality traits, coping style and specific consequences of stroke (objective cognitive performance, psychological distress and fatigue). Future research may evaluate whether there is also a relationship between subjective cognitive complaints and outcome variables like activities of daily living, quality of life, health care consumption and mortality.*

The results presented in Chapter 6 and 7 show that in patients with a mild severity of stroke, factors reflecting psychological distress (i.e., depression, anxiety and/or feelings of stress) and fatigue are stronger correlates of SCC during the first year after hospitalization than objective neuropsychological test results or stroke-related clinical measures. Perceived stress and depressive symptoms at 3 months after stroke were furthermore independently predictive of SCC at 12 months after stroke (Chapter 7). In addition, SCC tend to be persistent over time and are unlikely to disappear spontaneously from 3 months post-stroke to 1 year later (Chapter 7). It cannot be determined from the results in this dissertation whether the feelings of stress are related specifically with difficulties in dealing with stroke-specific consequences or whether they are related to general problems in life. The role of perceived stress in relation to SCC may be explored more thoroughly to be able to define important targets for behavioral and psychological interventions. Future research may focus on whether interventions aimed at reducing psychological distress, increasing psychological resilience and energy levels in the first months after stroke, are also accompanied by a reduction in the presence and/or impact of SCC after stroke. One of the effective elements in such interventions might be learning adequate compensation strategies and coping styles. It might be relevant to evaluate the effects of a more proactive coping style, over those of reactive coping styles, in dealing with stroke-specific problems and general problems in daily life. To explore changes in SCC over time and/or after an intervention, it is necessary to use an instrument that is sensitive to post-stroke SCC, but is also able to detect subtle changes in presence and impact of these complaints. The CLCE can be used for this purpose when completed with additional questions on subjective changes, but more sensitive tools that include meta-cognition as well as psychological adjustment to stroke will be necessary to optimally quantify post-stroke SCC.

Treatments targeting the contributing factors to post-stroke SCC may need to focus on psychological distress and post-stroke cognitive rehabilitation. Such interventions may not only improve SCC but also ADL and QoL. These effects may also translate into reduced health care consumption and increased survival (see Figure 1). This conceptual model requires confirmation in future research and may lead to multidisciplinary interventions that could potentially improve well-being after stroke.

The statistical analyses used in this dissertation relied primarily on linear regression models and analyses of variance (ANOVA). It is possible that complex techniques such as latent class analyses, multilevel analyses and/or growth curve analysis, would have revealed more subtle associations that could not be detected with regression and ANOVA. These statistical techniques will be of particular interest if additional repeated measures are included in the analyses. The present methods, however, facilitate reproducibility by other research teams (because results of complex techniques partially reflect sample-specific patterns in the data). The clinical interpretation of the findings is furthermore more explicit in the models used in the present studies compared to more complex techniques (e.g., it is difficult to 'observe' a latent variable in clinical practice).

4. Conclusions

This dissertation explores the prevalence, determinants and course of SCC during the first 12 months after stroke. The present studies show that SCC is prevalent in stroke survivors, in particular in the domains of memory, attention and concentration, executive functioning and language. Post-stroke SCC are associated with impaired objective cognitive functioning, psychological distress (i.e., depression, anxiety, perceived stress), fatigue and neuroticism. Symptoms of depression and perceived stress at 3 months after stroke independently predict the presence of SCC at 1 year follow-up. Furthermore, cumulative impairments of objective cognitive functioning may additionally result in post-stroke SCC.

Patient-reported SCC at 3 months after stroke require clinical attention because these SCC are unlikely to improve spontaneously. Evaluation of objective cognitive functioning using standard and ecologically valid neuropsychological tests combined with psychological evaluations for distress, fatigue and personality traits may identify new targets for interventions aimed at reducing the presence and impact of post-stroke SCC to ultimately improve well-being in these patients.

REFERENCES

1] Hartstichting. https://www.hartstichting.nl/hart-vaten/cijfers/beroerte. Accessed May 21, 2017.

2] Carod-Artal FJ, Egido JA. Quality of life after stroke: The importance of a good recovery. Cerebrovasc Dis. 2009;27 Suppl 1:204-214.

3] Cumming TB, Brodtmann A, Darby D, Bernhardt J. The importance of cognition to quality of life after stroke. J Psychosom Res. 2014;77:374-379.

4] Ellis C, Grubaugh AL, Egede LE. The association between major depression, health behaviors, and quality of life in adults with stroke. Int J Stroke. 2012;7:536-543.

5] Nys GM, van Zandvoort MJ, van der Worp HB, de Haan EH, de Kort PL, Jansen BP, et al. Early cognitive impairment predicts long-term depressive symptoms and quality of life after stroke. J Neurol Sci. 2006;247:149-156.

6] Tang WK, Lau CG, Mok V, Ungvari GS, Wong KS. Impact of anxiety on health-related quality of life after stroke: A cross-sectional study. Arch Phys Med Rehabil. 2013;94:2535-2541.

7] Johnson BH, Bonafede MM, Watson C. Short- and longer-term health-care resource utilization and costs associated with acute ischemic stroke. Clinicoecon Outcomes Res. 2016;8:53-61.

8] Feigin VL, Krishnamurthi RV, Parmar P, Norrving B, Mensah GA, Bennett DA, et al. Update on the Global Burden of Ischemic and Hemorrhagic Stroke in 1990-2013: The GBD 2013 Study. Neuroepidemiology. 2015;45:161-176.

9] Joo H, George MG, Fang J, Wang G. A literature review of indirect costs associated with stroke. J Stroke Cerebrovasc Dis. 2014;23:1753-1763.

10] Rigby H, Gubitz G, Phillips S. A systematic review of caregiver burden following stroke. Int J Stroke. 2009;4:285-292.

11] Brainin M, Tuomilehto J, Heiss WD, Bornstein NM, Bath PM, Teuschl Y, et al. Post-stroke cognitive decline: An update and perspectives for clinical research. Eur J Neurol. 2015;22:229-238, e213-226.

12] Moran GM, Fletcher B, Feltham MG, Calvert M, Sackley C, Marshall T. Fatigue, psychological and cognitive impairment following transient ischaemic attack and minor stroke: A systematic review. Eur J Neurol. 2014;21:1258-1267.

13] Makin SD, Turpin S, Dennis MS, Wardlaw JM. Cognitive impairment after lacunar stroke: Systematic review and meta-analysis of incidence, prevalence and comparison with other stroke subtypes. J Neurol Neurosurg Psychiatry. 2013;84:893-900.

14] Edwards JD, Jacova C, Sepehry AA, Pratt B, Benavente OR. A quantitative systematic review of domain-specific cognitive impairment in lacunar stroke. Neurology. 2013;80:315-322.

15] Cumming TB, Marshall RS, Lazar RM. Stroke, cognitive deficits, and rehabilitation: Still an incomplete picture. Int J Stroke. 2013;8:38-45.

16] de Haan EH, Nys GM, Van Zandvoort MJ. Cognitive function following stroke and vascular cognitive impairment. Curr Opin Neurol. 2006;19:559-564.

17] van Rijsbergen MW, Mark RE, de Kort PL, Sitskoorn MM. Subjective cognitive complaints after stroke: A systematic review. J Stroke Cerebrovasc Dis. 2014;23:408-420.

18] Maaijwee NA, Schaapsmeerders P, Rutten-Jacobs LC, Arntz RM, Schoonderwaldt HC, van Dijk EJ, et al. Subjective cognitive failures after stroke in young adults: Prevalent but not related to cognitive impairment. J Neurol. 2014;261:1300-1308.

19] Nijsse B, van Heugten CM, van Mierlo ML, Post MW, de Kort PL, Visser-Meily JM. Psychological factors are associated with subjective cognitive complaints 2 months post-stroke. Neuropsychol Rehabil. 2017;27:99-115.

20] van Rijsbergen MW, Mark RE, de Kort PL, Sitskoorn MM. The COMPlaints After Stroke (COMPAS) study: Protocol for a Dutch cohort study on poststroke subjective cognitive complaints. BMJ Open. 2013;3:e003599.

21] Broadbent DE, Cooper PF, FitzGerald P, Parkes KR. The Cognitive Failures Questionnaire (CFQ) and its correlates. Br J Clin Psychol. 1982;21 (Pt 1):1-16.

22] Ponds R, van Boxtel M, Jolles J. [The 'Cognitive Failure Questionnaire' as a measure of subjective cognitive functioning]. Tijdschrift voor neuropsychologie - diagnostiek, behandeling en onderzoek. 2006;1:37-45.

23] van Heugten C, Rasquin S, Winkens I, Beusmans G, Verhey F. Checklist for cognitive and emotional consequences following stroke (CLCE-24): Development, usability and quality of the self-report version. Clin Neurol Neurosurg. 2007;109:257-262.

24] van Rijsbergen MW, Mark RE, de Kort PL, Sitskoorn MM. Prevalence and profile of poststroke subjective cognitive complaints. J Stroke Cerebrovasc Dis. 2015;24:1823-1831.

25] van Rijsbergen MW, Mark RE, Kop WJ, de Kort PL, Sitskoorn MM. The role of objective cognitive dysfunction in subjective cognitive complaints after stroke. Eur J Neurol. 2017;24:475-482.

26] Stroop JR. Studies of interference in serial verbal reactions. J Expl Psychol. 1935;18:643-662.

27] Wilson B, Cockburn J, Baddeley A, Hiorns R. The development and validation of a test battery for detecting and monitoring everyday memory problems. J Clin Exp Neuropsychol. 1989;11:855-870

28] Galligan NG, Hevey D, Coen RF, Harbison JA. Clarifying the associations between anxiety, depression and fatigue following stroke. J Health Psychol. 2016;21:2863-2871.

29] van Heugten C, Rasquin S, Winkens I, Beusmans G, Verhey F. Checklist for cognitive and emotional consequences following stroke (CLCE-24): Development, usability and quality of the self-report version. Clin Neurol Neurosurg. 2007;109:257-262.

30] McKevitt C, Fudge N, Redfern J, Sheldenkar A, Crichton S, Rudd AR, et al. Self-reported long-term needs after stroke. Stroke. 2011;42:1398-1403.

31] Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. Classification and natural history of clinically identifiable subtypes of cerebral infarction. Lancet. 1991;337:1521-1526.

32] Liebermann D, Ostendorf F, Kopp UA, Kraft A, Bohner G, Nabavi DG, et al. Subjective cognitive-affective status following thalamic stroke. J Neurol. 2013;260:386-396.

33] Narasimhalu K, Wiryasaputra L, Sitoh YY, Kandiah N. Post-stroke subjective cognitive impairment is associated with acute lacunar infarcts in the basal ganglia. Eur J Neurol. 2013;20:547-551.

34] Flavell JH. Metacognition and cognitive monitoring. Am Psychol. 1979;34:906-911.

35] Hertzog C, Hultsch DF. Metacognition in adulthood and old age. In: Craik FIM, Salthouse TA, eds. The Handbook of Aging and Cognition. Mahwah, NJ, US: Lawrence Erlbaum Associates Publishers; 2000:417-466.

36] Aben L, Ponds RW, Heijenbrok-Kal MH, Visser MM, Busschbach JJ, Ribbers GM. Memory complaints in chronic stroke patients are predicted by memory self-efficacy rather than memory capacity. Cerebrovasc Dis. 2011;31:566-572.

37] Mol ME, Ruiter RA, Verhey FR, Dijkstra J, Jolles J. A study into the psychosocial determinants of

perceived forgetfulness: Implications for future interventions. Aging Ment Health. 2008;12:167-176.

38] McDougall GJ, Jr. A framework for cognitive interventions targeting everyday memory performance and memory self-efficacy. Fam Community Health. 2009;32:S15-26.

39] Valentijn SA, Hill RD, Van Hooren SA, Bosma H, Van Boxtel MP, Jolles J, et al. Memory self-efficacy predicts memory performance: Results from a 6-year follow-up study. Psychol Aging. 2006;21:165-172.

40] Brott T, Adams HP, Jr., Olinger CP, Marler JR, Barsan WG, Biller J, et al. Measurements of acute cerebral infarction: A clinical examination scale. Stroke. 1989;20:864-870.

41] Mahoney FI, Barthel DW. Functional evaluation: The Barthel Index. Md State Med J. 1965;14:61-65

42] de Haan R, Limburg M, Schuling J, Broeshart J, LJonkers L, van Zuylen P. [Clinimetric evaluation of the Barthel Index, a measure of limitations in activities of daily living]. Ned Tijdschr Geneeskd. 1993;137:917-921.

43] Duits A, Munnecom T, van Heugten C, van Oostenbrugge RJ. Cognitive complaints in the early phase after stroke are not indicative of cognitive impairment. J Neurol Neurosurg Psychiatry. 2008;79:143-146.

44] Hochstenbach J, Prigatano G, Mulder T. Patients' and relatives' reports of disturbances 9 months after stroke: Subjective changes in physical functioning, cognition, emotion, and behavior. Arch Phys Med Rehabil. 2005;86:1587-1593.

45] Winkens I, Van Heugten CM, Fasotti L, Wade DT. Reliability and validity of two new instruments for measuring aspects of mental slowness in the daily lives of stroke patients. Neuropsychol Rehabil. 2009;19:64-85.

46] Xiong YY, Wong A, Mok VC, Tang WK, Lam WW, Kwok TC, et al. Frequency and predictors of proxy-confirmed post-stroke cognitive complaints in lacunar stroke patients without major depression. Int J Geriatr Psychiatry. 2011;26:1144–1151.

47] Visser-Keizer AC, Meyboom-de Jong B, Deelman BG, Berg IJ, Gerritsen MJ. Subjective changes in emotion, cognition and behaviour after stroke: Factors affecting the perception of patients and partners. J Clin Exp Neuropsychol. 2002;24:1032-1045.

48] Davis AM, Cockburn JM, Wade DT, Smith PT. A subjective memory assessment questionnaire for use with elderly people after stroke. Clin Rehabil. 1995;9:238-244.

49] Tinson DJ, Lincoln NB. Subjective memory impairment after stroke. Int Disabil Stud. 1987;9:6-9.

50] Alt JA, Mace JC, Smith TL, Soler ZM. Endoscopic sinus surgery improves cognitive dysfunction in patients with chronic rhinosinusitis. Int Forum Allergy Rhinol. 2016;6:1264-1272.

51] Boyce-van der Wal LW, Volker WG, Vliet Vlieland TP, van den Heuvel DM, van Exel HJ, Goossens PH. Cognitive problems in patients in a cardiac rehabilitation program after an out-of-hospital cardiac arrest. Resuscitation. 2015;93:63-68.

52] Dufton BD. Cognitive failure and chronic pain. Int J Psychiatry Med. 1989;19:291-297.

53] Keizer AM, Hijman R, van Dijk D, Kalkman CJ, Kahn RS. Cognitive self-assessment one year after on-pump and off-pump coronary artery bypass grafting. Ann Thorac Surg. 2003;75:835-838.

54] Nijsse B, van Heugten CM, van Mierlo ML, Post MW, de Kort PL, Visser-Meily JM. Psychological factors are associated with subjective cognitive complaints 2 months post-stroke. Neuropsychol Rehabil. 2017;27:99-115.

55] Passier PE, Visser-Meily JM, van Zandvoort MJ, Post MW, Rinkel GJ, van Heugten C. Prevalence and determinants of cognitive complaints after aneurysmal subarachnoid hemorrhage. Cerebrovasc Dis. 2010;29:557-563.

56] Rasquin SM, van Heugten CM, Winkens L, Beusmans G, Verhey FR. [Checklist for the detection of cognitive and emotional consequences after stroke (CLCE-24)]. Tijdschr Gerontol Geriatr. 2006;37:112-116.

57] Wessels AM, Pouwer F, Geelhoed-Duijvestijn PH, Snel M, Kostense PJ, Scheltens P, et al. No evidence for increased self-reported cognitive failure in type 1 and type 2 Diabetes: A cross-sectional study. Diabet Med. 2007;24:735-740.

58] Wolters AE, Peelen LM, Veldhuijzen DS, Zaal IJ, de Lange DW, Pasma W, et al. Long-term self-reported cognitive problems after delirium in the intensive care unit and the effect of systemic inflammation. J Am Geriatr Soc. 2017;65:786-791.

59] Zlatar ZZ, Moore RC, Palmer BW, Thompson WK, Jeste DV. Cognitive complaints correlate with depression rather than concurrent objective cognitive impairment in the successful aging evaluation baseline sample. J Geriatr Psychiatry Neurol. 2014;27:181-187.

60] Whyte J, Grieb-Neff P, Gantz C, Polansky M. Measuring sustained attention after traumatic brain injury: Differences in key findings from the sustained attention to response task (sart). Neuropsychologia. 2006;44:2007-2014.

61] Postma IR, Bouma A, de Groot JC, Aukes AM, Aarnoudse JG, Zeeman GG. Cerebral white matter lesions, subjective cognitive failures, and objective neurocognitive functioning: A follow-up study in women after hypertensive disorders of pregnancy. J Clin Exp Neuropsychol. 2016;38:585-598.

62] Pollina LK, Greene AL, Tunick RH, Puckett JM. Dimensions of everyday memory in young adulthood. Br J Psychol. 1992;83 (Pt 3):305-321.

63] Payne TW, Schnapp MA. The relationship between negative affect and reported cognitive failures. Depress Res Treat. 2014;2014:396195.

64] Middelkamp W, Moulaert VR, Verbunt JA, van Heugten CM, Bakx WG, Wade DT. Life after survival: Long-term daily life functioning and quality of life of patients with hypoxic brain injury as a result of a cardiac arrest. Clin Rehabil. 2007;21:425-431.

65] Hohman TJ, Beason-Held LL, Resnick SM. Cognitive complaints, depressive symptoms, and cognitive impairment: Are they related? J Am Geriatr Soc. 2011;59:1908-1912.

66] Barker-Collo SL, Feigin VL, Lawes CM, Parag V, Senior H. Attention deficits after incident stroke in the acute period: Frequency across types of attention and relationships to patient characteristics and functional outcomes. Top Stroke Rehabil. 2010;17:463-476.

67] Burdett BR, Charlton SG, Starkey NJ. Not all minds wander equally: The influence of traits, states and road environment factors on self-reported mind wandering during everyday driving. Accid Anal Prev. 2016;95:1-7.

68] de Winter JC, Dodou D, Hancock PA. On the paradoxical decrease of self-reported cognitive failures with age. Ergonomics. 2015;58:1471-1486.

69] Wendel K, Risberg J, Pessah-Rasmussen H, Stahl A, Iwarsson S. Long-term cognitive functional limitations post stroke: Objective assessment compared with self-evaluations and spouse reports. Int J Rehabil Res. 2008;31:231-239.

70] Rabbitt P, Abson V. 'Lost and found': Some logical and methodological limitations of self-report questionnaires

as tools to study cognitive ageing. Br J Psychol. 1990;81 (Pt 1):1-16.
71] Stewart FM, Sunderland A, Sluman SM. The nature and prevalence of memory disorder late after stroke. Br J Clin Psychol. 1996;35 (Pt 3):369-379.
72] Martin C, Dellatolas G, Viguier D, Willadino-Braga L, Deloche G. Subjective experience after stroke. Appl Neuropsychol. 2002;9:148-158.
73] Lezak MD, Howieson DB, Loring DW. Neuropsychological Assessment. 4th Ed. New York, NY: Oxford University Press; 2004.
74] Spreen O, Strauss E. A compendium of neuropsychological tests administration, norms and commentary. 2nd Ed. New York, NY: Oxford University Press; 1998.
75] Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand. 1983;67:361-370.
76] Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: The PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. Jama. 1999;282:1737-1744.
77] Burton LJ, Tyson S. Screening for mood disorders after stroke: A systematic review of psychometric properties and clinical utility. Psychol Med. 2015;45:29-49.
78] Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: The GAD-7. Arch Intern Med. 2006;166:1092-1097.
79] Plummer F, Manea L, Trepel D, McMillan D. Screening for anxiety disorders with the GAD-7 and GAD-2: A systematic review and diagnostic meta-analysis. Gen Hosp Psychiatry. 2016;39:24-31.
80] Kroenke K, Wu J, Yu Z, Bair MJ, Kean J, Stump T, et al. Patient Health Questionnaire Anxiety and Depression Scale: Initial validation in three clinical trials. Psychosom Med. 2016;78:716-727.
81] Cosco TD, Doyle F, Ward M, McGee H. Latent structure of the Hospital Anxiety and Depression Scale: A 10-year systematic review. J Psychosom Res. 2012;72:180-184.
82] Cosco TD, Doyle F, Watson R, Ward M, McGee H. Mokken scaling analysis of the Hospital Anxiety and Depression Scale in individuals with cardiovascular disease. Gen Hosp Psychiatry. 2012;34:167-172.
83] Norton S, Cosco T, Doyle F, Done J, Sacker A. The Hospital Anxiety and Depression Scale: A meta confirmatory factor analysis. J Psychosom Res. 2013;74:74-81.
84] Sanderman R, Ormel J. [The Utrecht Coping List (UCL): Validity and reliability]. Gedrag Gezond. 1992;20:32-37.
85] van den Akker M, Buntinx F, Metsemakers JF, Knottnerus JA. Marginal impact of psychosocial factors on multimorbidity: Results of an explorative nested case-control study. Soc Sci Med. 2000;50:1679-1693.
86] Roesch SC, Aldridge AA, Huff TL, Langner K, Villodas F, Bradshaw K. On the dimensionality of the Proactive Coping Inventory: 7, 5, 3 factors? Anxiety Stress Coping. 2009;22:327-339.
87] Greenglass E, Fiksenbaum L, Eaton J. The relationship between coping, social support, functional disability and depression in the elderly. Anxiety, Stress Coping. 2006;19:15-31.
88] Aspinwall LG, Taylor SE. A stitch in time: Self-regulation and proactive coping. Psychol Bull. 1997;121:417-436.
89] Robertson IH, Ward T, Ridgeway V, Nimmo-Smith I. The Test of Everyday Attention. Bury St. Edmunds: Thames Valley Test Company; 1994.
90] Wilson BA, Evans JJ, Emslie H, Alderman N, Burgess P. The development of an ecologically valid test for assessing patients with a dysexecutive syndrome. Neuropsychol Rehabil. 1998;8:213-228.
91] Wilson BA, Shiel A, Foley J, Emslie H, Groot Y, Hawkins KA, et al. The Cambridge Prospective Memory Test. London: Harcourt; 2005.

SAMENVATTING
[SUMMARY]

INTRODUCTIE

Een Cerebro Vasculair Accident (CVA), ook wel beroerte genoemd, is wereldwijd een veel voorkomende aandoening. In Nederland worden jaarlijks circa 41.000 mensen getroffen door een CVA, wat neerkomt op 113 mensen per dag. Een CVA treedt op als de doorbloeding naar een deel van het brein wordt verstoord door een verstopping/afsluiting (herseninfarct) of scheuren (hersenbloeding) van een bloedvat. Ondanks dat de de behandelmogelijkheden in de acute fase de laatste jaren sterk zijn verbeterd, is een CVA nog altijd een van de belangrijkste oorzaken van overlijden en hebben mensen die het overleven vaak te kampen met blijvende beperkingen op fysiek, emotioneel en/of cognitief gebied. De mate van zelfredzaamheid en de kwaliteit van leven worden hierdoor vaak negatief beïnvloed.

Cognitieve problemen na een CVA zijn de laatste jaren regelmatig onderwerp geweest van wetenschappelijk onderzoek, mede omdat deze problemen deelname aan een revalidatieprogramma en de therapietrouw sterk kunnen belemmeren. De meeste studies hebben cognitieve problemen na een CVA onderzocht door met behulp van neuropsychologische tests, gericht op één of meerdere cognitieve domeinen, het cognitieve functioneren objectief te bepalen. Onderzoek laat zien dat bij 10 tot 82% van de patiënten cognitieve beperkingen aanwezig zijn na een CVA. Er is tot nu toe veel minder aandacht geweest voor de subjectieve ervaring van deze cognitieve problemen, oftewel: welke cognitieve problemen ervaren mensen zelf na hun CVA en in hoeverre zijn deze van invloed op hun dagelijkse leven? Deze subjectieve cognitieve klachten kunnen in kaart worden gebracht door middel van vragenlijsten en/of interviews. Uit de klinische praktijk en het kleine aantal studies over dit onderwerp, blijkt dat subjectieve cognitieve klachten vaak voorkomen na een CVA in zowel de acute, subacute als chronische fase. Meerdere factoren, onder andere objectief cognitief functioneren en een sombere stemming, lijken geassocieerd te zijn met het ervaren van subjectieve cognitieve klachten. Er is nog weinig bekend over hoe sterk deze relaties zijn en of er ook andere factoren betrokken zijn bij het ervaren van cognitieve klachten. Daardoor is het in de praktijk vaak moeilijk om adequate behandeling in te zetten om deze klachten te reduceren.

Doel van dit proefschrift

Het doel van dit proefschrift is het vergroten van de kennis over subjectieve cognitieve klachten bij volwassenen die een CVA hebben doorgemaakt. Daartoe wordt gebruik gemaakt van data verzameld in het kader van de COMPlaints After Stroke (COMPAS) studie, een prospectief cohort onderzoek waarin patiënten vanaf opname in het ziekenhuis tot twee jaar na hun CVA werden gevolgd op het gebied van onder andere objectief en subjectief cognitief functioneren. De bevindingen zoals beschreven in dit proefschrift betreffen de eerste resultaten van de COMPAS studie en richten zich op de prevalentie, determinanten en beloop van subjectieve cognitieve klachten gedurende het eerste jaar na een CVA.

VOORNAAMSTE BEVINDINGEN

Overzicht van de literatuur

Hoofdstuk 1 beschrijft de achtergrond van de COMPAS studie en de opbouw van dit proefschrift. In hoofdstuk 2 worden de resultaten beschreven van een systematisch literatuur onderzoek naar subjectieve cognitieve klachten bij CVA patiënten. Er werden in totaal 26 studies geïncludeerd. De studies verschillen erg van elkaar wat betreft de onderzochte CVA populatie (bijvoorbeeld een bepaald type CVA of alleen patiënten die zelfstandig thuis leven), tijd na een CVA waarop mensen werden geëvalueerd (variërend van enkele maanden tot enkele jaren na een CVA) en de instrumenten die werden gebruikt om subjectieve cognitieve klachten in kaart te brengen (een zelf ontwikkelde vragenlijst of een gevalideerd instrument, één of meerdere vragen per cognitief domein, etc.). Een van de voornaamste problemen betreft het ontbreken van consensus over de exacte definitie van subjectieve cognitieve klachten. Terwijl sommige studies zich richtten op subjectieve cognitieve klachten in het algemeen, onderzochten andere alleen die subjectieve cognitieve klachten die ook van invloed waren op het dagelijkse leven. Op basis van de literatuur werd daarom in hoofdstuk 2 de volgende definitie voorgesteld: subjectieve cognitieve klachten zijn cognitieve moeilijkheden of problemen die door mensen zelf gerapporteerd worden. Het is een psychologisch construct wat uit twee componenten bestaat, namelijk: *'content'* (oftewel 'inhoud', omvat de aard, het type cognitieve klacht, bijvoorbeeld subjectieve geheugen of concentratieproblemen) en *'worry'* (oftewel 'zich zorgen maken', geeft de invloed, de 'impact' van subjectieve cognitieve klachten aan in termen van interferentie van deze klachten in het dagelijkse leven, er zich aan ergeren en/of zich er zorgen over maken). Het onderscheid tussen deze twee componenten is van belang omdat iemand cognitieve problemen kan ervaren zonder hiervan hinder te ondervinden in het dagelijkse leven. Bovengenoemde definitie wordt in de overige hoofdstukken van dit proefschrift gebruikt.

Ondanks de verschillen tussen de studies, is de overkoepelende conclusie dat subjectieve cognitieve klachten frequent voorkomen na een CVA. De prevalentie van deze klachten varieert tussen de 28.6 en 92.0%. Klachten op het gebied van geheugen, mentaal tempo en concentratie worden hierbij het meeste gerapporteerd. Een andere bevinding van het literatuur onderzoek is dat er een matige overeenkomst is tussen de mening van patiënten en hun partners over de aanwezigheid en de ernst van cognitieve klachten bij de patiënt. Daarnaast blijken cognitieve klachten inconsistent geassocieerd te zijn met demografische en klinische kenmerken, huidige objectief cognitief functioneren en depressie. Er zijn echter aanwijzingen dat subjectieve cognitieve klachten na een CVA het toekomstig cognitief en emotioneel functioneren zouden kunnen voorspellen. Tenslotte lijken subjectieve cognitieve klachten toe te nemen met het verstrijken van de tijd na een CVA.

COMPAS studie

In hoofdstuk 3 wordt de rationale en het design van de COMPAS studie beschreven. Dit is de eerste prospectieve cohort studie die subjectieve cognitieve klachten gedurende de eerste twee jaar na een CVA systematisch onderzoekt. Daarbij wordt een uitgebreide batterij van subjectieve maten (zoals zelf-rapportage van subjectieve cognitieve klachten, depressie, angst, stress, vermoeidheid) en objectieve maten (zoals demografische en klinische kenmerken en neuropsychologisch onderzoek voor het objectief cognitieve functioneren) in kaart gebracht in de acute fase (tijdens de ziekenhuisopname) en op 3, 6, 12 en 24 maanden na het CVA. Daarbij wordt een vergelijking gemaakt tussen mensen met en mensen zonder een CVA.

De COMPAS studie beoogt de kennis over subjectieve cognitieve klachten na een CVA te vergroten, zodat clinici deze patiënten en hun naasten adequaat kunnen informeren over dergelijke klachten en gericht behandeladviezen kunnen geven. Uiteindelijk zal dit de kwaliteit van de nazorg voor mensen met een CVA verder verbeteren.

Tussen 2009 en 2012 werden patiënten die opgenomen werden voor een CVA in het Elisabeth-TweeSteden Ziekenhuis in Tilburg of in het Maxima Medisch Centrum in Veldhoven gevraagd deel te nemen aan de COMPAS studie. Via het sociale netwerk van deelnemers aan de studie en via andere betrokkenen, werd tevens een groep van mensen zonder een CVA gezocht. Deze vergelijkingsgroep zonder CVA biedt de mogelijkheid om te kunnen beoordelen of de klachten van de CVA patiëntengroep specifiek zijn voor een CVA. In totaal namen 211 CVA patiënten en 155 mensen in de vergelijkingsgroep deel aan de drie maanden meting van de COMPAS studie.

Prevalentie en profiel van subjectieve cognitieve klachten

In hoofdstuk 4 wordt de prevalentie en het profiel van subjectieve cognitieve klachten van patiënten drie maanden na een CVA beschreven en vergeleken met die van de groep mensen zonder CVA. Subjectieve cognitieve klachten werden onderzocht met behulp van twee instrumenten: de 'Cognitive Failures Questionnaire' (CFQ, een generieke vragenlijst) en de 'Checklist for Cognitive and Emotional consequences following stroke' (CLCE, een interview ontwikkeld specifiek voor mensen die een CVA hebben doorgemaakt). In lijn met wat eerder gevonden werd in de literatuur, kwamen subjectieve cognitieve klachten vaak voor na een CVA: 89.2% van de mensen rapporteerde drie maanden na hun CVA een of meerdere cognitieve problemen te ervaren. Deze problemen werden door 66.9% van de patiënten ook beoordeeld als hinderlijk in het dagelijkse leven (gemeten met de CLCE). In de niet-CVA groep waren de cijfers respectievelijk 65.2% en 40.7%.

Het profiel van subjectieve cognitieve klachten drie maanden na een CVA kenmerkte zich met name door klachten op het gebied van geheugen, aandacht en concentratie, executief functioneren en taal. Afhankelijk van het instrument wat gebruikt werd (CFQ of CLCE), verschilde de prevalentie en het profiel van klachten van dat wat gezien werd in de niet-CVA groep. Op de CFQ vragenlijst gaven patiënten *minder* vaak aan cognitieve problemen te ervaren dan de mensen in de vergelijkingsgroep en rapporteerden ze dezelfde mate van hinder. In het CLCE interview rapporteerden patiënten juist *meer* problemen dan de mensen in de vergelijkingsgroep op de gebieden geheugen, aandacht en concentratie, executief functioneren en taal en gaven ze vaker aan dat de problemen op gebied van aandacht ook hinderlijk waren. Op basis van deze resultaten en omdat de focus in dit proefschrift op de populatie CVA patiënten ligt, worden in hoofdstuk 5 tot en met 7 alleen de resultaten van het CLCE instrument in de patiëntengroep beschreven.

Relatie tussen objectief cognitief functioneren en subjectieve cognitieve klachten

In hoofdstuk 5 worden de resultaten gepresenteerd van het onderzoek naar de relatie tussen objectieve en subjectieve cognitieve problemen drie maanden na een CVA. Om het objectief cognitief functioneren te bepalen, werden in deze studie zowel conventionele neuropsychologische tests (zoals bijvoorbeeld de Stroop Kleur-Woord test) als meer recent ontwikkelde ecologisch valide tests (onder andere de Rivermead Behavioral Memory Test, RBMT) gebruikt. Subjectieve cognitieve klachten werden geïnventariseerd via de CLCE. De sterkste associatie tussen objectief cognitief functioneren en subjectieve cognitieve klachten werd gezien op de ecologisch valide geheugentest, de RBMT (voor de 'content' component: $\beta = -0.34$, $p = .001$; voor de 'worry' component: $\beta = -0.31$, $p = .002$).

Ook bleek er een significante associatie te bestaan tussen het aantal neuropsychologische tests wat als afwijkend werd beoordeeld (in vergelijking met bestaande normgroepen) en het rapporteren van subjectieve cognitieve klachten. Meer specifiek, wanneer patiënten drie maanden na hun CVA op meer dan acht neuropsychologische testen afwijkend scoorden (dat wil zeggen, lager scoorden dan de gepubliceerde cut-off waarde), nam het aantal subjectieve cognitieve klachten sterk toe.

Als de cognitieve domeinen afzonderlijk worden bekeken, verschillen de resultaten voor de 'content' en de 'worry' component van subjectieve cognitieve klachten enigszins van elkaar. Voor de 'content' component werden significante associaties gevonden tussen objectief cognitief functioneren en subjectieve cognitieve klachten op gebied van geheugen, executief functioneren en taal. Voor de 'worry' component werden significante associaties gezien op de domeinen geheugen, mentaal tempo/aandacht en executief functioneren.

Alhoewel de associaties tussen het aantal objectieve problemen en de mate van subjectieve cognitieve klachten significant zijn, is de sterkte van deze samenhang onvoldoende om de hoge prevalentie van subjectieve cognitieve klachten drie maanden na een CVA te verklaren. Het is daarom waarschijnlijk dat andere factoren ook een rol spelen in het hebben van subjectieve cognitieve klachten na een CVA.

Psychologische factoren en subjectieve cognitieve klachten

Hoofdstuk 6 beschrijft de resultaten van het onderzoek naar de mate waarin depressie, angst, stress en vermoeidheid geassocieerd zijn met subjectieve cognitieve klachten drie maanden na een CVA. Deze psychologische variabelen hadden alle een significante correlatie met subjectieve cognitieve klachten (Pearson's r waarden variëren tussen de 0.38 en 0.45; p-waardes allemaal < .001). Met behulp van multivariate statistische analyses werd aangetoond dat deze relaties significant bleven na correctie voor de mogelijke samenhang met leeftijd, geslacht, IQ, ernst van het CVA, mate van objectieve cognitieve problemen en algemeen dagelijks functioneren (β waarden variëren tussen de 0.35 en 0.39, alle p-waardes < .001). Het is mogelijk dat deze psychologische variabelen een algemeen niveau van spanning ('distress') weergeven.

Ook wordt in hoofdstuk 6 onderzocht of bovengenoemde relaties met subjectieve cognitieve klachten beïnvloed worden door (onderliggende) persoonlijkheidsfactoren en coping stijlen. De 'content' component van subjectieve cognitieve klachten bleek onafhankelijk geassocieerd te zijn met vermoeidheid ($\beta = 0.26$, $p = .003$), neuroticisme ($\beta = 0.21$, $p = .05$) en het aantal objectieve cognitieve problemen ($\beta = 0.20$, $p = .03$). Onafhankelijke relaties met de 'worry' component werden gevonden voor angst ($\beta = 0.27$, $p = .01$), stress ($\beta = 0.25$, $p = .01$) en het aantal objectief cognitieve problemen ($\beta = 0.33$, $p = .001$). Demografische kenmerken, klinische kenmerken en coping stijl bleken geen significante relatie te hebben met subjectieve cognitieve klachten.

Deze resultaten laten zien dat psychologische spanning ('distress') en vermoeidheid samenhangen met het ervaren van subjectieve cognitieve klachten drie maanden na een CVA. Daarnaast vormen persoonlijkheidsfactoren, neuroticisme in het bijzonder, een belangrijke schakel in de associatie tussen psychologische spanning en subjectieve cognitieve klachten na een CVA. Deze cross-sectionele analyses kunnen echter niet aangeven wat oorzaak en wat gevolg is. Er zijn daarom in het volgende hoofdstuk eveneens longitudinale analyses uitgevoerd om te onderzoeken welke factoren van belang zijn voor het ontstaan en/of voortduren van subjectieve cognitieve klachten.

Het beloop van subjectieve cognitieve klachten na een CVA

In hoofdstuk 7 wordt het beloop van subjectieve cognitieve klachten tussen drie en twaalf maanden na een CVA beschreven. Bij de 155 patiënten die aan beide meetmomenten deelnamen, bleek dat deze klachten relatief stabiel bleven over de tijd. Wanneer op groepsniveau werd gekeken, waren de gemiddelde CLCE scores bij de follow-up meting vrijwel identiek aan de scores op de drie maanden meting (drie versus twaalf maanden 'content' = 3.3 ± 2.4 versus 3.3 ± 2.6, $p > 0.99$; 'worry' = 1.9 ± 2.2 versus 2.1 ± 2.5, $p = .28$). Op het individuele niveau van de patiënt had meer dan de helft van de patiënten ('content' 56.8% en 'worry' 64.5%) een stabiele score (dat wil zeggen, minder dan een standaard deviatie verschil, gelijk aan nul punten of één punt verandering over de tijd). De resultaten van de 'reliable change index' bevestigden de stabiliteit van de subjectieve cognitieve klachten: minder dan 10% van de patiënten met een CVA vertoonde een significante verandering over de tijd (acht mensen gingen significant achteruit, drie mensen gingen significant vooruit).

Voorspellers van subjectieve cognitieve klachten

In hoofdstuk 7 wordt ook onderzocht of er drie maanden na een CVA factoren zijn aan te wijzen die de aanwezigheid van subjectieve cognitieve klachten op twaalf maanden na een CVA kunnen voorspellen. Het hebben van subjectieve cognitieve klachten op drie maanden bleek de sterkste voorspeller voor het hebben van deze klachten op twaalf maanden ('content' $\beta = 0.54$, $p < .001$; 'worry' $\beta = 0.57$, $p < .001$). Voor de 'content' component had daarnaast een algemeen gevoel van stress ($\beta = 0.23$, $p = .003$) op drie maanden na het CVA eveneens een voorspellende waarde voor cognitieve klachten op twaalf maanden. Voor de 'worry' component was dit de aanwezigheid van depressieve symptomen drie maanden na het CVA ($\beta = 0.23$, $p = .003$). Demografische en klinische kenmerken en objectieve cognitieve problemen drie maanden na een CVA waren geen onafhankelijke voorspellers voor subjectieve cognitieve klachten bij de follow-up meting.

KLINISCHE IMPLICATIES EN SUGGESTIES VOOR TOEKOMSTIG ONDERZOEK

De resultaten in dit proefschrift laten zien dat de prevalentie van subjectieve cognitieve klachten gedurende het eerste jaar na een CVA hoog is (schatting > 89% op drie maanden en > 80% op twaalf maanden). Deze hoge prevalentie leidt bij de helft tot tweederde van de patiënten tot problemen in het dagelijks leven. De klachten blijven in het eerste jaar stabiel over de tijd. Dit benadrukt het belang voor clinici om alert te zijn op de aanwezigheid van dergelijke klachten gedurende de eerste maanden na een CVA. Screening op de aanwezigheid van subjectieve cognitieve klachten tijdens de reguliere follow-up controles kun hierbij behulpzaam zijn. Bij voorkeur wordt voor een dergelijke screening een instrument gebruikt wat specifiek gericht is op het inventariseren van cognitieve klachten na een CVA, maar wat ook gevoelig is voor subtiele veranderingen in deze klachten over de tijd. De CLCE kan hiervoor gebruikt worden, mits het wordt aangevuld met vragen over subjectieve veranderingen in klachten en/of impact over de tijd. Daarbij dient wel bedacht te worden dat niet iedereen die cognitieve problemen in het dagelijkse leven ervaart, hierover zal klagen. Wanneer mensen voor deze problemen kunnen compenseren en/of ze ondervinden er geen hinder van bij hun activiteiten, zullen mensen uit zichzelf deze problemen wellicht niet rapporteren. Een differentiatie tussen subjectieve cognitieve problemen die wél versus problemen die geen impact hebben op het dagelijkse leven zou daarom nuttig kunnen zijn. In toekomstig onderzoek en in de klinische praktijk zou het relevant kunnen zijn om mensen specifiek te vragen of er wel/geen behoefte is aan hulp voor hun subjectieve cognitieve klachten. Ook wanneer mensen zelf geen cognitieve klachten rapporteren, betekent het niet dat deze er ook daadwerkelijk niet zijn. Naasten kunnen een heel andere mening hebben dan de patiënt zelf. Ontkenning, cognitieve beperkingen of een vermindering van ziekte-inzicht bepalen mede of iemand wel/geen cognitieve problemen zal ervaren en/of rapporteren. Wanneer er een meningsverschil is tussen de patiënt en diens naaste(n), kan eventueel een programma voor familieleden gericht op het leren omgaan met de factoren die maken dat de patiënt geen klachten rapporteert, aangewezen zijn.

Meerdere factoren kunnen bijdragen aan het hebben van subjectieve cognitieve klachten na een CVA. Objectieve cognitieve beperkingen kunnen een rol spelen. Door middel van neuropsychologisch onderzoek kan nagegaan worden of de gerapporteerde cognitieve klachten ook geobjectiveerd kunnen worden. Aanbevolen wordt om hierbij zowel standaard tests alsook ecologisch valide tests te gebruiken. De kans om een associatie te vinden tussen objectief en subjectief cognitief functioneren lijkt het grootste te zijn op gebied van geheugen, maar toekomstig onderzoek moet uitwijzen of dit ook geldt voor andere domeinen als meer ecologisch valide tests worden gebruikt (bijvoorbeeld de 'Test of Everyday Attention' en de complete 'Behavioral Assessment of the Dysexecutive Syndrome' test batterij). De resultaten in dit proefschrift laten zien dat er mogelijk een drempel van objectieve cognitieve problemen is waarboven patiënten ook duidelijk meer cognitieve klachten gaan rapporteren.

Naast objectieve cognitieve beperkingen, spelen ook andere psychologische factoren mogelijk een rol in het ervaren van subjectieve cognitieve klachten na een CVA. Factoren die psychologische spanningen ('distress') reflecteren (zoals depressie, angst en/of stress) en vermoeidheid zijn sterk gerelateerd aan subjectieve cognitieve klachten gedurende het eerste jaar na een CVA. Demografische en klinische kenmerken (zoals ernst van het CVA) blijken daarentegen nauwelijks tot geen rol te spelen. Een kenmerk van de huidige steekproef is dat de ernst van een CVA relatief beperkt was en het is daarom mogelijk dat bij ernstige CVA er een sterker verband tussen het objectieve en subjectieve cognitief functioneren gevonden wordt. Op basis van de resultaten in dit proefschrift kan niet worden vastgesteld of de stress gevoelens specifiek te maken hebben met het omgaan met de gevolgen van het CVA en/of met algemene

problemen horende bij het leven. De rol van stress in het ervaren van subjectieve cognitieve klachten na een CVA kan in de toekomst verder onderzocht worden om mogelijke aanknopingspunten voor gedragsmatige en psychologische interventies te bepalen.

Wanneer een patiënt drie maanden na een CVA subjectieve cognitieve klachten rapporteert, is de kans groot dat deze klachten op twaalf maanden ook nog aanwezig zullen zijn. Het ervaren van symptomen van een depressie en een algemeen gevoel van stress drie maanden na een CVA zijn daarbij onafhankelijke voorspellers voor het ervaren van subjectieve cognitieve klachten een jaar na een CVA. De resultaten in dit proefschrift suggereren dat interventies gericht op het reduceren van psychologische 'distress', het vergroten van de psychologische veerkracht en het energie niveau gedurende de eerste maanden na een CVA, mogelijk ook gepaard gaan met een reductie in het aantal subjectieve cognitieve klachten en/of de impact van deze klachten op het dagelijkse leven. Dit verdient echter nader onderzoek. Een van de effectieve elementen van dergelijke interventies zou het aanleren van adequate coping strategieën en coping stijlen kunnen zijn. Hierbij kan onderzocht worden of het aanleren van meer proactieve copingstijlen, naast reactieve coping stijlen, effectief is in het omgaan met CVA specifieke problemen en algemene problemen van het dagelijkse leven.

CONCLUSIES

In dit proefschrift worden de prevalentie, de determinanten en het beloop van subjectieve cognitieve klachten gedurende de eerste twaalf maanden na een CVA onderzocht. De resultaten van de studies laten zien dat deze klachten vaak voorkomen na een CVA, met name op het gebied van geheugen, aandacht en concentratie, executief functioneren en taal. Subjectieve cognitieve klachten na een CVA zijn hoofdzakelijk geassocieerd met psychologische 'distress' (depressie, angst, stress), vermoeidheid en neuroticisme en in mindere mate met objectieve cognitieve problemen. Op de lange duur blijkt dat symptomen van depressie en stress drie maanden na een CVA van belang zijn als voorspellers voor het rapporteren van subjectieve cognitieve klachten twaalf maanden na een CVA.

Subjectieve cognitieve klachten gerapporteerd door patiënten drie maanden na een CVA verdienen klinische aandacht aangezien deze klachten zeer waarschijnlijk niet spontaan zullen verbeteren gedurende het eerste jaar. Het in kaart brengen van objectief cognitief functioneren (met behulp van zowel standaard als meer ecologisch valide tests) in combinatie met evaluatie van psychologische 'distress', vermoeidheid en persoonlijkheid kan mogelijke aanknopingspunten voor behandeling opleveren, met als uiteindelijke doel de aanwezigheid en impact van subjectieve cognitieve klachten te verminderen en daarmee het welzijn van deze patiënten te verbeteren.

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Mariëlle

OVER DE AUTEUR

ABOUT THE AUTHOR

Mariëlle van Rijsbergen werd geboren op 7 juni 1982 te Terneuzen, Nederland. In 2000 behaalde zij haar VWO diploma aan het Zeldenrust-Steelandcollege te Terneuzen en ging ze Psychologie, met als specialisatie Neuropsychologie, studeren aan Tilburg University. Na haar doctoraal diploma (cum laude) in 2006 werd ze toegelaten tot de Master Medische Psychologie aan Tilburg University. Deze opleiding rondde ze met een subspecialisatie in de Neuropsychologie af in 2008 (cum laude), waarna ze startte met haar promotieonderzoek bij het Center of Research on Psychology in Somatic diseases (CoRPS) en het departement Cognitive Neuropsychology bij Tilburg University. Op dit moment werkt Mariëlle als psycholoog en zelfstandig ondernemer waarbij zij zich specifiek richt op de begeleiding van volwassenen met niet-aangeboren hersenletsel.

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