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Resuscitate the heart and remember the brain

A prospective observational study of cognitive outcome after Out-of-Hospital Cardiac arrest

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A dissertation for the degree of Philosophiae Doctor – December 2015

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Tromsø, Norway 2015

Acknowledgements

This PhD project was performed at the University Hospital of North Norway (UNN-HF). The project was a collaborative project between the departments of rehabilitation, cardiology and radiology at UNN-HF and the Faculty of Health Sciences at the UIT, The Arctic University of Norway. The research project was financially funded by the Norwegian Extra Foundation for Health and Rehabilitation through Extra funds, the University Hospital of North Norway (UNN-HF), and the Faculty of Health sciences at the UIT, The Arctic University of Norway. Further, the Norwegian Health Authorities Northern Region funded the last 6 months of this project so that this thesis could be finished.

This project was the result of the hard work of many people to whom I am eternally grateful.

First, I would like to thank my main supervisor, Audny Anke for her willingness to supervise this project, for instructive supervision, for always being available, caring and encouraging. For positive promotion of this project both within and outside the context of UNN-HF and for all her efforts that made the completion of this project practically possible.

Chair of Department of Cardiology, Pål M. Tande should be acknowledged as the initiator of this project. His interest in survivors' quality of life was the starting point of both this research project and the clinical follow-up service for cardiac arrest survivors recently developed at UNN-HF. Thank you for supporting me throughout this project.

Many thanks to co-supervisor Torgil R. Vangberg for your patience with the data collection and for helping me with statistics and presenting data. I look forward to future projects.

Very personal and special thanks to Per M. Aslaksen for practical help with project management, good discussions, unwavering support and optimism.

Many grateful thanks to my collaborators and co-authors of the articles Christoph Schäfer, Kristina Larsby and Lena Norli. Thank you all for your contributions in the different stages of this project and for your time spent working on this research project despite busy clinical schedules.

Many thanks to the health secretaries in the rehabilitation ward, especially Rønnaug Johnsen for practical help with the data collection and the Division of Neurosciences, Orthopedics and Rehabilitation Services at UNN-HF for hosting me during the project period.

Last, but not least, my sincere appreciation goes to the study participants who volunteered their time and mental labor for this research project. Thank you.

Tromsø 22.12.2015
Marte C. Ørbo

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List of research reports

This thesis is based on the following articles, which will be referred to in the text by their Roman numerals:

Article I

Ørbo M, Aslaksen PM, Larsby K, Norli L, Schäfer C, Tande PM, Vangberg TR, Anke A. **Determinants of cognitive outcome in survivors of out-of-hospital cardiac arrest.** Resuscitation. 2014 Nov;85(11):1462-8.

Article II

Ørbo M, Aslaksen PM, Larsby K, Schäfer C, Tande PM, Vangberg TR, Anke A. **Relevance of cognition to health related quality of life after survival from out-of-hospital cardiac arrest.** Journal of Rehabilitation Medicine 2015; 47: 860–866

Article III

Ørbo M, Aslaksen PM, Larsby K, Schäfer C, Tande PM, Anke A.
Does cognitive outcome change from 3-12 months in survivors from out-of-hospital cardiac arrest? Submitted September 2015.

Summary

Background and aims: Out-of-Hospital Cardiac Arrest (OHCA) can cause hypoxic-ischemic brain injury, which may lead to persistent cognitive impairment and disability. The main aims of the present project was to investigate whether demographic-, resuscitation- and medical characteristics were associated with cognitive outcome, address the relevance of cognitive functioning to health-related quality of Life (HRQL) and the stability in cognitive outcome from 3-12 months after resuscitation.

Methods: Only adult survivors with few additional risk factors for cognitive impairments other than the OHCA and cardiac arrest due to a cardiac etiology were included prospectively at the University hospital of North Norway (2010-2013). To examine cognitive functions neuropsychological tests were used. Symptoms of anxiety and depression were evaluated with the Hospital Anxiety and Depression Scale (HADS) and HRQL with the Short-Form (SF)-36 questionnaire. The results for survivors were compared to published normative data correcting for demographic characteristics. Of the 129 survivors identified, 79 survivors were eligible according to inclusion criteria at 3 months. The three empirical studies in this thesis are based on an inclusion rate of 61% (N=48).

Results: Among the demographic, medical and resuscitation characteristics assessed for associations with cognitive outcome in the first paper (N=45), shorter coma duration and having received hypothermia treatment were associated with better cognitive results 3 months after resuscitation. Longer coma duration was associated with worse outcome across all neuropsychological tests, whereas receiving hypothermia treatment was associated with better outcomes of specific tests of memory and executive functions. Significant cognitive impairments were found in tests of memory, executive- and psychomotor functioning, as well as a global cognitive score. Impairment rates on cognitive tests ranged from 9% to 31 %. Rates of self-reported anxiety and depression symptoms were generally low.

Only good outcome survivors, who were functionally independent and were living in their regular homes without organized support at least 2 months after OHCA were included in the second paper (N=42). Significant associations between neuropsychological tests and the SF-36 were found. Lower performance on tests of psychomotor functioning was associated with

worse physical HRQL, whereas memory test performance was associated with worse mental HRQL in both correlational analyses and in general linear models controlling for coma duration, age and education level. 30% of the good outcome survivors showed impairments on test for delayed recall memory and 10% for psychomotor speed and executive functions, respectively. Not all impairments were mild. None reported symptoms of depression above the cut-off on the HADS. General observations for the whole group indicate that physical HRQL was lower than normative standards, but that mental HRQL was not.

The specific aims of the third paper (N=33) were to measure changes in cognitive functions from 3 to 12 months assessments and to explore whether cognitive impairment at 3 months were related to poorer reports of HRQL, return to work or emotional problems at 12 months. Although significant, but small improvements were observed in domains of executive and visual memory functioning, survivors classified as cognitively impaired at 3 months (33%) were still in the impaired range at 12 months. Lower cognitive functioning at 3 months were correlated with poorer results in the main physical component of SF-36 at 12 months, but not with poorer results in the mental component. Poorer scores was observed on the mental SF-36 component from 3 to 12 months, in parallel with a slight increase in HADS scores. Only one patient with cognitive impairment detected at 3 months had returned to work at 12 months.

<u>Conclusions:</u> Cognitive tests representative of memory, psychomotor and executive functions were significantly impaired and poorer cognitive functioning was associated with longer duration of coma after resuscitation at 3 months. Changes in cognitive outcomes from 3 to 12 months were limited, and this result suggests that early assessment by far can proximate later results, keeping it open that clinical meaningful change can occur at least in some survivors over even longer time spans. Significant associations observed between worse cognitive functioning and poorer HRQL of life at both 3 and 12 months may suggest that the cognitive impairments can cause long-term disability even in good outcome survivors with ability to function independently soon after resuscitation and discharge from the hospital. The generalizability of the results are limited by the small sample, loss-to-follow up and selection bias toward patients with favorable prognosis. The results are descriptive and not causal. Future studies of cognitive outcome should include coma duration as a

control variable and pay attention to cognitive dysfunction as an explanatory variable for lower HRQL. The importance of the project lies in its clinical implication showing that more survivors are in need of follow-up for cognitive impairments than is detected in regular care. Follow-up assessment after OHCA should be provided and cognitive functioning addressed systematically in addition to other patient-relevant outcomes.

Sammendrag norsk (summary in Norwegian)

Prehospital hjertestans fører hyppig til død grunnet hjerneskade. Med riktig førstehjelp og tilgang til avansert medisinsk behandling kan død og hjerneskade unngås. Alvorlig funksjonstap hos overlevere er uvanlig og de fleste skrives ut til hjemmet og forventes å leve som før. Hos disse er omfanget av vedvarende kognitive og emosjonelle senfølger usikkert og betydningen av kognitiv svikt for helserelatert livskvalitet i liten grad undersøkt tidligere.

En prospektiv, empirisk observasjonsstudie ble gjennomført på Universitetssykehuset i Tromsø (2010-13). Totalt ble 129 pasienter utskrevet etter prehospital hjertestans av kardiale årsaker i denne perioden. Stringente eksklusjonskriterier ble brukt for å selektere deltakere med få andre risikofaktorer for kognitiv svikt og emosjonelle problemer enn hjertestans. Av 79 egnede deltakere ble 48 (61%) undersøkt og inkludert i studien. Standardiserte og normerte nevropsykologiske tester ble brukt for kartlegging av kognitive funksjoner 3 og 12 måneder etter hjertestans. I tillegg inkluderte undersøkelsen to selvrapporteringsskjema; ett for angst- og depresjonssymptomer (HADS) og ett for helserelatert livskvalitet (SF-36). Deltakernes resultater ble sammenliknet med publiserte normative data.

Resultatene er rapportert i 3 artikler med henholdsvis 45, 42 og 33 deltakere. Noen grad av kognitiv funksjonsnedsettelse ble sannsynliggjort hos nesten halvparten av de undersøkte ved 3 måneder. Lette til moderate kognitive problemer var det vanligste. Tester for verbale - og visuelle hukommelsesfunksjoner, reguleringsfunksjoner og psykomotorisk tempo var signifikant nedsatt. For et mindretall ble mer omfattende kognitiv svikt avdekket. Lengre tid fra hjertestans til pasienten våknet fra koma var signifikant assosiert med dårligere prestasjoner på alle kognitive tester etter 3 måneder. Liten bedring ble observert i kognitive

funksjoner fra 3 til 12 måneder. Dårligere kognitive testresultater ved 3 måneder var assosiert med lavere selvrapportert helserelatert livskvalitet ved 3 og 12 måneder. Deltakerne rapporterte få psykiske plager, men noe mer ved 12 enn ved 3 måneder. Deltakere med kognitiv svikt ved 3 måneder hadde mindre sannsynlighet for å gå tilbake til jobb det første året etter gjenoppliving. Utvalget i studien er lite. Inklusjonskriteriene begrenser generaliserbarheten. Anbefalinger for videre forskning på kognitiv funksjon etter hjertesans kan være at fremtidige studier bør kontrollere for tid i koma og at kognitiv funksjon bør vurderes inkludert som mål på helserelatert livskvalitet i denne pasientgruppen. I klinisk praksis bør overlevere etter prehospital hjertestans tilbys systematisk etterundersøkelse som inkluderer vurdering av mulige kognitive og emosjonelle senfølger. Tilpassede rehabiliteringstiltak vil kunne øke muligheten for mestring, aktivitet og deltakelse i hverdagen.

Introduction

Survival from any type of injury to the brain can become more challenging because of alterations in physical, neurologic, cognitive, and emotional and behavioral characteristics, which may influence, according to the severity of consequences, an individual's ability to live independently, interact socially or work (Finset & Krogstad, 2002).

Cognitive alterations means deterioration in a person's ability to remember, learn, speak, solve problems, plan or concentrate, and they are common consequences of any disease or injury affecting the brain. During a cardiac arrest, the brain receives less oxygen and nutrients, and this causes permanent damage in the brain within a few minutes unless cardiopulmonary resuscitation is initiated immediately with consecutive medical treatment (Busl & Greer, 2009; Garcia-Molina et al., 2006).

Severe neurological or extensive cognitive impairments are a real concern in victims of OHCA, but are not the typical outcome, and the majority of survivors are discharged to their normal home environment after resuscitation and varying lengths of hospital stays (Drysdale, Grubb, Fox, & O'Carroll, 2000; Nolan, 2011). Clinical relevant, but subtler changes in cognitive, emotional, social or and functions may not be detected in the hospital setting unless they are severe or actively screened for (N. R. Grubb, O'Carroll, Cobbe, Sirel, & Fox, 1996; V. R. Moulaert, Verbunt, van Heugten, & Wade, 2009). Cardiac arrest survivors are considered cardiac patients, and therefore, assessments by neurologists, neuropsychologists or rehabilitation therapists are not regularly provided during hospitalization or in regular follow-ups after discharge (Drysdale et al., 2000; V. R. Moulaert et al., 2011). Furthermore, the daily-life challenges accompanying more subtle brain injury may not be manifest in the patient within the hospital setting or before he or she returns to work, where more challenging tasks are demanded (V. R. Moulaert, van Haastregt, Wade, van Heugten, & Verbunt, 2014; V. R. Moulaert et al., 2011; V. R. Moulaert et al., 2009; V. R. Moulaert, Wachelder, Verbunt, Wade, & van Heugten, 2010; Tiainen et al., 2015).

Recently, recommendations for post-resuscitation care published by the European Resuscitation Council in 2015 include a novel section on rehabilitation for OHCA survivors focusing on non-cardiac rehabilitation needs (Nolan et al., 2015). Added to the previous recommendations is that systematic screening for cognitive and emotional problems should be provided to all survivors upon discharge from the hospital and sometimes after discharge in a follow-up consultation. The purpose of this recommended screening is to target the OHCA survivors in need of further referral to existing rehabilitation programs, further assessment or treatments. Specific recommendations for assessment and follow-up are provided at https://www.erc.edu/ (ERC, 2015).

At the time of conceptualizing this thesis, we were not able to locate any hospital in Norway that routinely provided follow-up consultations for possible cognitive problems after OHCA. Furthermore, OHCA survivors are rarely seen as in-patients in the rehabilitation ward or as outpatients by clinical neuropsychologists at the University Hospital of North Norway. Receiving inpatient rehabilitation is a gross measure of injury severity. The main focus of the present project is on the survivors who are not in need of inpatient rehabilitation after resuscitation. After various lengths of hospital stays, these patients are discharged to their own homes. Follow-up consultations are provided according to cardiac needs without further considerations of possible cognitive dysfunction.

During the data-collection for this clinical research project, the OHCA survivors at our hospital were given more clinical attention than they had received previously. Neuropsychological assessments of cognitive outcomes have been provided as a clinical service to all survivors regardless of research participation, and although not a part of the research project, a telephone-based follow-up routine has been implemented in the rehabilitation ward.

In the following sections, the background information considered most relevant for this thesis is outlined, followed by a brief presentation of the specific aims of the empirical studies and a presentation of the procedure and methods used for assessment as well as a review of the three articles. Finally, a more general discussion of the limitations and the results in the three manuscripts, complementing the discussions in the published articles is given, with the aim of drawing implications for clinical practice and future research.

Background information

Out of hospital cardiac arrest (OHCA)

Cardiac arrest is defined as the cessation of productive cardiac mechanical activity defined by the absence of palpable pulse and spontaneous respiration which may be reversible but will lead to death in the absence of immediate interventions (Eisenberg & Mengert, 2001). The incidence and prevalence estimates of OHCA are based on the epidemiology studies using the Utstein template for uniform reporting (I. Jacobs et al., 2004). In Europe, OHCA has an incidence of 86.4 per 100,000 inhabitants (Atwood, Eisenberg, Herlitz, & Rea, 2005). Cardiac arrest can occur for a variety of reasons, but the most common cause is a cardiac origin of coronary artery disease (Zheng, Croft, Giles, & Mensah, 2001). The probability of OHCA increases with increasing age (Straus et al., 2004) and is more prevalent in males (Herlitz et al., 2004). Survival rates for OHCA are generally low, but also highly variable between countries and regions (P. S. Chan, McNally, Tang, & Kellermann, 2014). Recent estimates suggest improved survival rates and many life-years gained after ventricular fibrillation OHCA of cardiac cause (Lindner, Vossius, Mathiesen, & Soreide, 2014). Recent years improvements in survival are attributed to the implementation of standardized treatment guidelines, an increase in by-stander resuscitation and the availability of automated external defibrillators (Cronberg et al., 2015; Hansen et al., 2015; Wissenberg et al., 2013). Survival to discharge is the most common end-point in most scientific studies, and longer time delays in follow-up are often regarded as long-term outcomes (L. B. Becker et al., 2011).

OHCA related brain injury and neurologic prognosis

Cardiac arrest can result in injury to all organ systems. The brain, however, is particularly vulnerable to deprivation of blood supply because of its high metabolic demand (Anderson & Arciniegas, 2010; Busl & Greer, 2009). The mechanisms of damage to the brain during and after cardiac arrest are referred to as hypoxic and hypoxic-ischemic (Busl & Greer, 2009). Hypoxia refers to a reduction in oxygen supply or utilization alone, whereas ischemia describes a reduction in blood supply, which leads not only to decreased oxygen delivery but also to limited or no removal of toxic cellular metabolites. The complex biochemical mechanisms that occur in a circulatory arrest contributes to neuronal damage and death during and after restoration of systemic circulation through delayed neuronal death caused by reperfusion injury and microcirculatory impairment (Busl & Greer, 2009; Madl & Holzer, 2004). Neurologic outcomes are diverse and range from full recovery to brain death and persistent vegetative states, long-term or permanent coma, seizures and myoclonus, or subtle sensory-motor, cognitive and affective changes (Lim, Alexander, LaFleche, Schnyer, & Verfaellie, 2004; Longstreth, Inui, Cobb, & Copass, 1983; Lu-Emerson & Khot, 2009; F. C. Wilson, Harpur, Watson, & Morrow, 2003).

In survivors of OHCA, at least in the western part of the world, severe neurologic impairment is rare, with as many as 86% achieving good long-term neurological outcomes according to the commonly used cerebral performance categories (CPC) (L. B. Becker et al., 2011; Peberdy et al., 2003). The CPC scale measures outcomes on a 1-5 point scale with 1 and 2 indicating good neurologic recovery and 3-5 indicating poor recovery (L. B. Becker et al., 2011). The CPC scale has been criticized for being too unsophisticated and too optimistic, without the ability to describe the difficulties that the patient may experience with every-day life activities (L. B. Becker et al., 2011). In 2002, two large randomized control trials showed that inducing mild hypothermia for 12-24 hours at 32-34°C in comatose OHCA victims after ventricular fibrillation (VF) resulted in improved survival rates and better neurological outcomes compared with patients with no temperature management (Bernard et al., 2002; Holzer et al., 2002). Consequently, hypothermia treatment was implemented in standard treatment protocols in many places (L. B. Becker et al., 2011).

In 2007, a randomized control trial showed no significant effect of hypothermia treatment on cognitive outcomes measured with a broad battery of neuropsychological tests 3 months after OHCA. Cognitive deficits were found in 34% of the survivors with good CPC scores (Tiainen et al., 2007). In the 2011 consensus statement for primary outcomes for resuscitation science studies, the American Heart Association emphasized that a wide range of outcome measures should be used in research to characterize the broad possibilities of impairments and disabilities following OHCA (L. B. Becker et al., 2011; Raina, Rittenberger, Holm, & Callaway, 2015).

Long-term cognitive outcome after OHCA

Cognitive problems assessed by self-reports months and years after out-of-hospital cardiac arrest (OHCA) have previously been associated with increased dependency in daily living, social isolation, reduced health related quality of life and elevated caregiver burden (Middelkamp et al., 2007; V. R. Moulaert et al., 2014; V. R. Moulaert et al., 2015; V. R. Moulaert et al., 2009; Wachelder et al., 2009).

Moulaert et al (2009) systematically reviewed studies informative of cognitive impairments after OHCA from 1980 to 2006. Twenty-eight articles were found, including measures of cognitive outcome from at least one cognitive test administrated three or more months after OHCA. The cognitive impairment rates in the studies ranged from 6% to 100%. The authors emphasized the need for more studies describing cognitive outcomes after OHCA with neuropsychological tests (V. R. Moulaert et al., 2009).

Neuropsychological assessment methods provides performance-based measures of an individual's cognitive abilities. Tests designed to measure cognitive functions such as memory, attention, language and perception are typically administrated to a patient in a standardized manner and the patient's results are compared to a large reference group with similar demographic characteristics. A cognitive impairment is observed when results on a certain number of tests falls below normative standards and is below what could be expected of from the individual prior to brain injury or disease. Neuropsychological assessment methods have shown to be clinically necessary despite advancements in brain imaging technology, as an individual can have significant cognitive and functional impairments in absence of structural lesions on imaging or structural lesions without functional and cognitive impairments (P. D. Harvey, 2012; M. H. Lezak, D.B., Bigler, E.D. & Tranel, D. , 2012; Strauss, Sherman, & Spreen, 2006).

Other outcome instruments for neurologic, cognitive, social and functional prognosis are important, but may lack sensitivity and psychometric validity to detect mild-moderate cognitive changes and to differentiate between spared and intact cognitive functions in survivors of OHCA with good neurologic recovery. Furthermore, the association between self-reported cognitive complaints and the results for neuropsychological has remained a subject to debate and has not been empirically tested in survivors of OHCA (V. R. Moulaert et al., 2011; V. R. Moulaert et al., 2009; V. R. Moulaert et al., 2010).

There are also problems noted in the previous neuropsychological studies of cognition (Anderson & Arciniegas, 2010; Lim & Alexander, 2010; V. R. Moulaert et al., 2009). Issues involving indifference to the etiology of hypoxia, mixing the populations of in- and out-of-hospital arrest, carbon monoxide poisoning, drowning, strangulation or respiratory deficiency are common in these studies (Caine & Watson, 2000; Lim & Alexander, 2010; V. R. Moulaert et al., 2009; Peskine, Rosso, Picq, Caron, & Pradat-Diehl, 2010; Prohl, Bodenburg, & Rustenbach, 2009; Prohl et al., 2007; B. A. Wilson, 1996). The cause of a hypoxic event and cause of cardiac arrest may be important to studies of cognition, as the different etiologies produces brain damage by different mechanisms and may affect prognosis and functional outcomes differently (Anderson & Arciniegas, 2010; Busl & Greer, 2009; Caine & Watson, 2000; Lim & Alexander, 2010; V. R. Moulaert et al., 2009). Furthermore, several neuropsychological studies have selected participants with severe deficits in one or more area to describe a specific phenomenon, or have selected only the patients referred for inpatient rehabilitation, thus having worse cognitive outcomes than average (Lim & Alexander, 2010; Lim, Verfaellie, Schnyer, Lafleche, & Alexander, 2014; V. R. Moulaert et al., 2009; Quamme, Yonelinas, Widaman, Kroll, & Sauve, 2004).

When Moulaert et al (2009) assessed the methodological quality of studies with prospective inclusion and neuropsychological tests of cognition for methodological quality, only three neuropsychological studies were identified as good indicators of the frequency of cognitive outcome after OHCA. These 3 studies reported cognitive impairments in 42% (van Alem, de Vos, Schmand, & Koster, 2004), 48% (Sauve, Walker, Massa, Winkle, & Scheinman, 1996), and 50% (Roine, Kajaste, & Kaste, 1993) of patients.

In more recent studies (Alexander, Lafleche, Schnyer, Lim, & Verfaellie, 2011; Cronberg, Lilja, Rundgren, Friberg, & Widner, 2009; Tiainen et al., 2007; Torgersen et al., 2010; van Alem et al., 2004), it is concluded that 30 – 50% have cognitive impairments, most cognitive impairments after OHCA are mild and eventually moderate, with severe impairments being rather unusual. As Buanes et al (2015) summarized, if 30% of cardiac arrest victims survive with cognitive impairments in Europe every year, this would indicate that 25000-40000 survivors have some degree of cognitive impairment every year (Buanes et al., 2015).

<u>Cognitive profile</u>

Isolated memory deficits were long considered the core cognitive impairment after OHCA, attributed to the relative increased vulnerability of hippocampus CA 1 neurons to hypoxic events (Anderson & Arciniegas, 2010; Lim et al., 2004). Neuropsychological studies that have addressed more than memory functions have shown that isolated problems with memory seldom occur after OHCA (Anderson & Arciniegas, 2010; Lim et al., 2004). Volumetric cerebral imaging of long-term survivors from OHCA has not confirmed focal hippocampal injury for memory impairments (N.R. Grubb et al., 2000; Horstmann et al., 2010). Studies involving neuropsychological tests combined with advanced cerebral MRI findings in long term survivors of OHCA are sparse because a large proportion of those who survive OHCA longer than a month may receive an implanted cardioverter defibrillator (ICD), which is impossible to combine with the highly electro-magnetic MRI environment (Horstmann et al., 2010). To date, there are few imaging studies of sufficient scientific quality that provide information on the brain correlates of functional impairments and their recovery in long-term survivors after OHCA (Hahn, Geocadin, & Greer, 2014).

OHCA is assumed to potentially affect the brain globally, causing widespread cognitive impairments. Several subcortical and cortical areas are prone to hypoxic–ischemic events according to the leading hypothesis (Lim & Alexander, 2010). The cerebral areas assumed to be at greatest risk are not consistently described among studies, but the areas regularly mentioned are the basal ganglia, thalamic nuclei, hippocampus and cortical matter around watershed areas and the cerebellum (Caine & Watson, 2000). The relative vulnerability of neurons in these areas comes from a higher metabolic rate or demand for oxygen and nutrients and from the location in vascular boarder zones (Caine & Watson, 2000; Moody, Bell, & Challa, 1990).

Across most neuropsychological studies of cognition in OHCA survivors of cardiac arrest from a cardiac cause, it is suggested that mild and moderate cognitive sequela occur in a combined pattern of problems with aspects of memory and psychomotor/fine-motor function or memory, attention and executive functions (Alexander et al., 2011; Lim & Alexander, 2010; B. A. Wilson, 1996). For less mildly affected survivors, it is suggested that an increasing number of additional cognitive domains show impairment (Lim & Alexander, 2010). Some have suggested that an increasing number of cognitive domains will show impairment according to the severity of memory and psychomotor deficits (Lim & Alexander, 2010); however, visuospatial, perceptual and executive functioning problems are described as impaired in other studies (Alexander et al., 2011; Roine et al., 1993). In one study, executive impairments were found more frequently than memory impairments (Tiainen et al., 2007). In survivors with more severe cognitive impairment, no cognitive domain seems to escape risk where language, general orientation and general intelligence, working memory, poor insight into own deficits and behavior disturbances are described as deficits (Alexander et al., 2011; Caine & Watson, 2000; Prohl et al., 2009; Pusswald, Fertl, Faltl, & Auff, 2000; Roine et al., 1993; Sauve, Walker, et al., 1996; Tiainen et al., 2007; van Alem et al., 2004). The number of studies equipped to explain differences in neuropsychological profiles in subgroups according to outcome severity are sparse (Lim & Alexander, 2010). In 2011 new research guidelines for resuscitation outcomes studies recommended including at least one neuropsychological test for attention, executive and memory functions (L. B. Becker et al., 2011).

Determinants of cognitive outcome

Longer coma duration has been systematically linked to the severity of neurologic prognosis (Lim & Alexander, 2010; Longstreth et al., 1983) and the extent of cognitive complaints after OHCA (Middelkamp et al., 2007). Coma duration as a determinant of neuropsychological tests performance has received little empirical attention (Goossens & Moulaert, 2014; V. R. Moulaert et al., 2009). However, Sauve et al (1996) and Alexander et al (2011) have supported this hypothesis. Alexander et al (2011) found a coma duration of 1-3 days to increase the likelihood of only mild deficits compared with coma duration of 3 –7 days. Other time dependent resuscitation variables such as the time to return of spontaneous circulation (ROSC) have not been systematically linked to neuropsychological test performance in previous research (N. R. Grubb et al., 1996; van Alem et al., 2004).

Other empirically tested explanatory variables for the variation in neuropsychological test performance are sparse (V. R. Moulaert et al., 2009). In one study, age under 25 years was positively correlated with better cognitive outcomes (Dougherty, 1994). However, another study found no influence of age, sex or education for neuropsychological measures (Prohl et al., 2009). Neurochemical markers (S-100 protein) have successfully predicted later cognitive test performance in two studies (N. R. Grubb et al., 2007; Prohl et al., 2009). Furthermore, very early cognitive assessment at bed-site were predictive of impairment at 6 months in one study (Prohl et al., 2009), while significant improvements were observed upon repeated testing from bed-site to 3 months after in a study by Sauve et al (Sauve, Doolittle, Walker, Paul, & Scheinman, 1996). Depression or hypothermia treatment has not been significantly linked to outcomes on neuropsychological test (V. R. Moulaert et al., 2009; Tiainen et al., 2007).

Cognitive Recovery

Many survivors may be confused and show poor memory and orientation in the days after awakening from coma (Sauve, Walker, et al., 1996). The real concern is the permanent cognitive impairments over months and years after OHCA. Only a few neuropsychological studies have assessed cognition over time with more than one time point of assessment (Drysdale et al., 2000; Harve et al., 2007; Sauve, Doolittle, et al., 1996; Sauve, Walker, et al., 1996). Across the studies, both improvements and deterioration in cognitive functioning are described, but it is generally concluded is that most recovery occurs during the first 3-6 months after OHCA and that very little improvement can be measured thereafter (Lim et al., 2014; Roine et al., 1993; Sauve, Doolittle, et al., 1996; Sauve, Walker, et al., 1996). It is however, also suggested that a good outcome, once achieved, it can be maintained for several years (Harve et al., 2007). Furthermore, recovery after brain injury is not isolated to performance on neuropsychological tests. Other measures of functional independency, neurologic impairments, depression, anxiety or quality of life may produce different conclusions about recovery over time (Dougherty, 1994; Larsson, Wallin, Rubertsson, & Kristofferzon, 2014; Raina et al., 2015).

Affective symptoms

Intervention to treat problems with anxiety and depression should have high priority in populations with cardiac disease (Hopkins, Kesner, & Goldstein, 1995; Roine et al., 1993; Sauve, Walker, et al., 1996; Sunnerhagen, Johansson, Herlitz, & Grimby, 1996). Affective symptoms should be assessed together with cognitive impairments after OHCA, as their clinical manifestation may share overlapping characteristics, and depression may influence neuropsychological test results (Caine & Watson, 2000; Richards & Ruff, 1989). Further affective problems and cognitive impairments require different treatment approaches (Nancy Frasure-Smith, Lespérance, & Talajic, 1995; Golinkoff & Sweeney, 1989). Affective symptoms and disorders have received less attention than cognitive impairments after OHCA (Schaaf et al., 2013). Studies reports different rates of symptoms of anxiety, depression and PTSD, which is typically addressed with screening scales (Elliott, Rodgers, & Brett, 2011; Lilja, Nilsson, et al., 2015; V. R. Moulaert et al., 2015; V. R. Moulaert et al., 2010; Schaaf et al., 2013). Different rates can be due to differences in the time points of measurement and the measurements themselves (Dougherty, 1994; Larsson et al., 2014; Schaaf et al., 2013) as well as the heterogeneity in the OHCA populations studied. Elevated affective symptoms after OHCA may be due to premorbid disorders, reactions to cardiac arrest, functional disability or intensive care unit stay (Arawwawala & Brett, 2007; B. A. Wilson, 2013). Some studies have described emotion- related changes as a consequence of brain injury, such as apathy or personality changes, which may readily be misunderstood as primarily affective disorders in clinical practice (Caine & Watson, 2000). Self-reported symptoms of depression and anxiety have shown relevance for health-related quality of life after OHCA (V. R. Moulaert et al., 2010).

Cognitive impairment and disability

It has been questioned by previous studies whether the cognitive impairments frequently observed on neuropsychological tests after OHCA translate into disability (Cronberg et al., 2009; Torgersen et al., 2010). The relationship between impairment and disability is not straightforward in the sense that worse impairment always causes more disability. For instance, a mild memory deficit can cause no trouble to an OHCA survivor who is retired, but for a lawyer, the same memory deficit may be the reason that he cannot continue his job (Andelic et al., 2010; Raina et al., 2015).

The question about impairments and disability also reflects an increase in the interest and awareness of measuring patient centered outcomes after trauma and disease (Elliott et al., 2011). Patient-centered outcomes have in common that they aim to capture the individual's experience of disability and therefore provides important information in addition to outcome measures focused on functional impairments. Within a patient-centered approach, it is also important to know the factors that compromise health perceptions and cause disability (Andelic et al., 2010; Elliott et al., 2011; V. R. Moulaert et al., 2010; Polinder, Haagsma, van Klaveren, Steyerberg, & van Beeck, 2015).

"Health-related quality of life (HRQL) refers to how health impacts on an individual's ability to function and his or hers perceived well-being in physical, mental and social domains of life" (J. E. Ware et al., 1994; J. E. Ware, Jr. & Sherbourne, 1992). HRQL is measured with questionnaires concerning how the patient perceive that his or her health enables the performance of physical, psychological and social activities. Low HRQL scores could therefore be viewed as a measure of disability or capacity for activity and participation in daily life.

The studies of HRQL after OHCA show that averaged reports of HRQL are good or close to population normative data (Elliott et al., 2011). However, individual survivors with lowered scores are of particular concern to health care workers. Understanding the variables, associated with reduced HRQL, can guide assessment and treatment procedures (Arawwawala & Brett, 2007; V. R. Moulaert et al., 2010).

Prior to our second article, traditional neuropsychological tests of cognition were not explored as explanatory variables for the commonly used, generic Short-Form (SF)-36 questionnaire of HRLQ after OHCA. However, neuropsychological measures of cognition are shown to account for a significant proportion of variance in HRQL after TBI (Andelic et al., 2010) and stroke (Hochstenbach, Anderson, van Limbeek, & Mulder, 2001). Furthermore, Moulaert et al (2010) found that more cognitive complaints, fatigue and symptoms of anxiety and depression were associated with poorer SF-36 results after OHCA, suggesting that OHCA-related cognitive impairment causes disability. Cronberg et al (2009) concluded that although neurological and cognitive impairments were frequently detected on neuropsychological tests 6 months after cardiac arrest, they did not translate into poor HRQL scores on the rather crude measure of HRQL EQ-5D. However, lower EQ- 5D scores were not assessed for associations with the tests showing impairments. One article prior to 2014 have explored the associations between performance on a computerized neuropsychological tests and the HRQL questionnaire SF-36 in a sample of long-term survivors with good CPC scores (Torgersen et al., 2010). Although half of the sample had at least mild cognitive impairments, the study concluded that there was no significant association between cognitive impairments and SF-36. The findings suggest that cognitive impairments measured after OHCA does not cause disability. However, the cognitive test results were correlated only with a single question on the SF-36 questionnaire. The one question selected concerns a change in general health status during the past year. This question may be perceived by patients as related to physical health only and is not representative of the multiple dimensions of HRQL. Further, CANTAB has shown only modest correlations with traditional neuropsychological tests (P. J. Smith, Need, Cirulli, Chiba-Falek, & Attix, 2013).

Aims of the thesis

This thesis consist of three articles with the following specific aims:

Article I

*To describe how the OHCA survivors, characterized by few risk factors for cognitive impairment other than the OHCA and resuscitation, perform on a broad battery of neuropsychological tests 3 months after successful resuscitation compared to large, demographically matched samples of published normative data.

* Investigate if characteristics of the cardiac arrest and resuscitation can predict cognitive performance 3 months later, when controlling for affective symptoms, comorbidity and demographic variables.

Article II

*To explore if and how performance on neuropsychological tests of memory, psychomotor speed and executive functioning are associated with Health related quality of life (HRQL) in a group of OHCA survivors that were discharged early form the hospital to their own homes, not receiving any assessment or rehabilitation for possible cognitive impairments.

Article III

*To investigate if cognitive functioning change from three to twelve months after resuscitation.

*To assess if cognitive status at 3 months after OHCA is related to reduced HRQL after 12 months.

Methods and materials

Study setting and recruitment

The study was empirical and observational. The data collection was performed prospectively over a 3-year period (2010-13). A single hospital was involved. The identification of survivors, recruitment and assessment took place in a clinical setting. Thus, methods for recruitment and assessment were conformed to fit this context.

The University Hospital of North Norway (UNN-HF) situated in Tromsø in subarctic Norway at 69 °N latitude. It is the largest regional hospital of the northern health region in Norway, covering the three northernmost counties with a combined population of 456,000 distributed over a geographic area of 112,000km^2. The hospital serves smaller hospitals in a regional manner. Despite a challenging geography and settlement, the region has a well-developed public Emergency Medical System (EMS). Despite long prehospital evacuation times in time-critical medical emergencies survival rates after OHCA, survival rates in our region are estimated to be comparable to other regions in Norway and Europe (Hilmo, Naesheim, & Gilbert, 2014; Lien Nilsen, Bo, Rasmussen, Haanaes, & Gilbert, 2011).

The cardiac ward at UNN-HF has on a yearly basis 10 000 outpatient consultations, 1200 surgical procedures and 3500 invasive assessment procedures related to cardiac conditions. It is estimated that approximately 45 OHCA survivors are discharged alive from the cardiac ward at the hospital every year. The hospital's protocols confirms to current evidence-based guidelines for advanced treatment and management of OHCA victims (Nolan et al., 2015) and treatment includes advances procedures such as hypothermia treatment (HT) implantations of internal cardio defibrillators (ICD), percutaneous coronary interventions (PCI), catheter ablations and coronary artery bypass grafting (CABG). The current study did not involve any changes to the medical care for the OHCA patients.

There was no formal register for OHCA at the time of conducting this study. Due to non-systematic registration of the exact incidence of OHCA in our region, numbers about deaths due to OHCA before or during hospital admission is not available. In standard care at the hospital, not all OHCA survivors are seen again at the hospital after discharge from the cardiac ward but receives follow-ups for cardiac matters at local hospitals. Since cognitive assessment or follow-up for non-cardiac problems after OHCA was not part of the routine for survivors at our hospital when this study was conceptualized, we had to establish a new clinical routine for identification and prospective inclusion to the research project so that the survivors could be invited to the research project that took place in the Rehabilitation ward. The aim was to identify all OHCA survivors at the time of discharge from the cardiac ward and electronically referrer the patient to the rehabilitation ward so that an invitation to the research project could be sent by mail to the patient after he or she had returned home.

Inclusion and exclusion criteria

We chose to include only adult (age span 18-85) OHCA survivors with a cardiac arrest from a cardiac origin. The inclusion and exclusion criteria were designed to obtain control over several other risk factors for cognitive impairment than OHCA and resuscitation. This is generally common in neuropsychological studies of brain disease and injury populations, and has been done in previous studies of neuropsychological functioning after OHCA (Alexander et al., 2011; Roine et al., 1993; Tiainen et al., 2007; van Alem et al., 2004)**.** Different form some previous studies of neuropsychological functioning after OHCA, we did not exclude participants that had regained consciousness within the first hours of hospital admission or prior to hospital admission (Alexander 2011, Roine 1993, Tiainen 2007) and we used no cut-off for inclusion based on time to ROSC (Tiainen et al., 2007) or rapid Emergency Medical Services (EMS) response (van Alem et al., 2004). Inclusion and exclusion criteria for the three articles are shown in Table 1. Note that in Article II there were some additional exclusion criteria applied based on functioning.

Table 1. Inclusion and exclusion criteria applied in study I-III.

Inclusion	Exclusion
All articles:	All articles:
Adults aged 18-85.	Age below 18 or above 85.
First time, normothermic cardiac arrest outside the hospital with assumed cardiac origin.	In-hospital arrest.
Discharged alive from the cardiac ward at UNN-HF in the study period.	OHCA due to other causes than cardiac.
Volunteered to the clinical follow up and research participation.	Died before 3 months.
Fluent in Norwegian language, written and verbal.	Not eligible of neuropsychological assessment due to severe brain injury caused by the OHCA, hearing/sight impairments, non-fluency in Norwegian language or paralyses in upper extremities.
Normal sight and hearing or corrected to normal with glasses or hearing aids.	Premorbid level of functioning and comorbidity: previous cardiac arrest, previous neurological disease, brain injury, or serious psychiatric disease (schizophrenia, bipolar disorder or severe depression), substance abuse disorder, included alcohol abuse, learning disabilities, developmental disorders, dementia. Further participant were excluded if they had serious ongoing diseases such as cancer or renal failure.
Eligible of a valid neuropsychological assessment after approximately 3 months.	Other reasons for exclusion Does not wish to participate in research.
Additional for Article 2: Received no rehabilitation after discharge from the cardiac ward, functional independent prior to and after OHCA, living at home at least 2 months after OHCA.	Does not agree to the clinical follow-up.
Additional for Article 3: Participated in study 1 and was eligible of repeating the assessment at 12 months post resuscitation.	Not able to give informed consent.
	Pain or low motivation.
	Additional for Article 2:
	Received inpatient rehabilitation.
	Prolonged hospitalization.
	Not independent in living 1 month before the follow-up.
	Not completed the SF-36

General procedure

The procedure for data-collection in this study was an outpatient, face-to-face clinical neuropsychological assessment with a battery of neuropsychological tests and two survey forms; the Hospital Anxiety and Depression Scale (HADS) and the Short Form (SF)-36 performed at approximately 3 and 12 months after successful resuscitation Authorized clinical neuropsychologists performed the assessments in an office equipped for neuropsychological testing at the hospital. The assessors were not blinded to the treatment characteristics of the patients. The procedure lasted from 2-3 hours including breaks, the anamnestic interview, test administration, filling out questionnaires and talking to survivors and sometimes relatives. There was no control group, but the participants results on the neuropsychological tests and questionnaires administered were compared to published normative data from large samples of healthy people with similar demographic characteristics.

Both premorbid function and health as well as physical and mental health and behavior at the time of assessment can influence results on neuropsychological tests (Heilbronner et al., 2009; M. H. Lezak, D.B., Bigler, E.D. & Tranel, D. , 2012). Prior to testing the examiner made sure the patient was motivated, in no pain, had slept and eaten, were on no sedatives and comprehended the goal of the assessment. Patients were encouraged to communicate if he needed breaks during the test session to enhance optimal and valid performance on cognitive tests (Strauss et al., 2006). Anamnestic information was collected from the patient.

Demographic and medical data obtained from patient interview and hospital journals

The data collected from questionnaires, cognitive tests and medical journals are numeric and quantitative. Demographic variables coded in the data-file included gender, age, years of education, independent living and employment situation both before OHCA and at the time of follow-up. The living situation of the patient was coded as “independent living” both when living with a partner and not. Both part and full time return to work was coded as “returned to work”.

Information about medical and resuscitation variables used as predictors and covariates in the analyses in the three articles were obtained from patient`s medical journals at the hospital. The hospital records variables related to resuscitation according to the Utstein template (Ringdal et al., 2008). The following information was obtained and coded in the data file: Witnessed or unwitnessed OHCA, time from collapse to return of spontaneous circulation (ROSC) in minutes, if by-stander resuscitation was initiated (yes/no), first presented cardiac rhythm on scoop (VF/AF/Asystole), number of shocks from defibrillator, time to ambulance arrival from collapse (in minutes), the cardiac cause of the arrest (infarction, arrhythmia, unknown), length of coma (in hours) or awake upon admission (yes/no), any previously diagnosed cardiac conditions, diabetes (yes/no). Treatment variables coded were: hypothermia (yes/no), Percutaneous coronary intervention (PCI) (yes/no), Coronary arterial bypass grafting (CABG) (yes/no), implanted cardio defibrillator (ICD) (yes/no), neurological deficits if any (motor or sensory impairments), length of hospital stay at the intensive care unit (in days) and at the cardiac ward (in days). These data were selected based on previous articles and discussion with the cardiologists involved in this project.

Description of tests and questionnaires

Neuropsychological tests

Only neuropsychological tests that are commonly applied in clinical practice by neuropsychologists were used (M. D. Lezak, 2004; M. H. Lezak, D.B., Bigler, E.D. & Tranel, D. , 2012; M. R. Schoenberg & Scott, 2011; Strauss et al., 2006). The selection of neuropsychological tests was based on a practical clinical approach confirming to common practice guidelines for assessment of cognitive functions by Norwegian clinical neuropsychologists http://www.nevropsyk.org/fag/veileder-klinisk-nevropsykologi (NPF, 2015) and tests frequently used locally at our hospital by the neuropsychologists employed there, no novel methods or were used. The selection of neuropsychological tests also reflects considerations of the psychometric quality of tests, construct validity, tests-retest reliability, ecological validity and considerations of the suitability of tests for a heterogeneous group of OHCA patients (wide age span and a-priori hypothesized large heterogeneity in cognitive performance), availability of published tests in Norwegian language, a recognition of what tests were used in previous studies of OHCA survivors to facilitate comparison with previous studies (Alexander et al., 2011; Lim et al., 2004; Lim et al., 2014; Roine et al., 1993; Tiainen et al., 2007; van Alem et al., 2004), and availability of normative data to facilitate the analysis of clinically significant levels of impairments. Computerized scoring procedures were used for all tests, except for the Wechsler's Abbreviated Scale of Intelligence (WASI).

Please see Appendix 1 for an overview of the neuropsychological test used in the three articles and how the tests and subtest were grouped into composite scores representing different cognitive domains.

Wechsler's Abbreviated Scale of Intelligence (WASI)

The Wechsler's Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) provides a brief measure of general cognitive ability and IQ. The WASI was published in USA in 1999 as a brief screening measure for intelligence (IQ). WASI consists of two verbal subtests (Similarities and Vocabulary) and two non-verbal subtests (Matrix reasoning and Block Design). General cognitive ability (IQ scores) can be calculated from all four subtests or from two subtests (Vocabulary and Matrix reasoning). The tests normative sample were 2245 participants in the age range from 6-89 years and was considered to be representative for the US population. A Norwegian translation of the instructions, scoring guidelines and verbal stimulus material was published in 2007, after performance of pilot studies that found the translated version to have reasonable statistical qualities and good fit with the original American version (Sundet, Ørbeck, Brager-Larsen, & Bang Nes, 2000; Ørbeck & Sundet, 2007). The subtests gives information about verbal comprehension and perceptual organization, which is considered as two of the main components of general cognitive abilities in the Wechsler tests (M. H. Lezak, D.B., Bigler, E.D. & Tranel, D. , 2012). A recent quality assessment of the WASI in Norwegian samples concluded that the normative data that were obtained in US samples during the 1990s might overestimate cognitive abilities when employed in Norwegian settings (Siqveland J, 2014). This is similar to findings from US studies (Axelrod, 2002). Wechsler tests, including the WASI total IQ and especially the verbal IQ are often used as estimates of premorbid level of functioning (Carlozzi et al., 2011). Generally, IQ is a predictor of academic achievements, social mobility, job performance (Deary, Penke, & Johnson, 2010). Furthermore, WASI total IQ score and the verbal IQ are shown to be predictive for return to work after brain injury (Roberts, Coetzer, & Blackwell, 2004). Test-retest reliability is shown to be excellent for all three measures of IQ, total IQ, verbal IQ and performance IQ (Ryan et al., 2003), but there are no data for test-retest reliability in Norwegian samples (Siqveland, 2014).

California Verbal Learning Test 2. Edition (CVLT-II)

The California Verbal Learning Test-II (CVLT-II) is a list learning task that is considered a valid measure of verbal learning and memory (Alexander, Stuss, & Fansabedian, 2003). It includes 5 learning trials, immediate and delayed free and cued recall trials as well as a recognition trial. The psychometric properties have been well established and validate its use in varied brain injured populations (D. Delis, Kramer, Kaplan, & Ober, 2000). This revised version of the CVLT was published in the USA in 2000. It was officially published in Norwegian in 2004 with the original US normative data ranging from 16 to 89 years (Lundervold & Sundet, 2004). It comes in standard and alternative versions. The standard version was used in the present project. All subtests with the exception of the forced recognition trial was administrated in the present project. Parallel versions exists to be used with repeated testing of the same persons to minimize training effects, but was not used in the present study (Delis D, 2000). Studies in Norwegian samples have suggested that the US normative data for CVLT-II are applicable for Norwegian settings (Bosnes, 2007). The CVLT II is found to be comparable to the Rey Auditory Verbal Learning Test (RAVLT) (M. L. Jacobs & Donders, 2007) and the list learning task in the Wechsler Memory Scale (WMS) (McDowell, Bayless, Moser, Meyers, & Paulsen, 2004). List learning tasks are used frequently in previous studies of cognitive functioning after OHCA, but the RAVLT more used compared to the CVLT. The RAVLT not published in Norwegian. A study comparing RAVLT and CVLT found high correlations between raw scores, but discrepancies in normative data produced lower standard scores on the CVLT compared to the RAVLT on similar tasks (Stallings, Boake, & Sherer, 1995).The CVLT-II has high test-retest reliability with test-retest correlations about 0.80 (Woods, Delis, Scott, Kramer, & Holdnack, 2006). Practice effects are shown to be relatively high when the standard form is administered at both occasions (Cohens *d* in the range 0.4-1.3), but comparable to other measures of verbal memory when test-retest intervals are approx. 30 days (Benedict, 2005). At longer test-retest intervals, smaller practice effects are anticipated (Woods et al., 2006). The CVLT-II is considered a valid measure of verbal memory and has shown ability to differentiate between employed versus work disabled subject (Stegen et al., 2010): Still, isolated CVLT-II scores should be used with caution in order to determine whether an acquired memory impairment is present or not (M. L. Jacobs & Donders, 2008). In healthy elderly, CVLT-II scores are shown to be correlated with functional connectivity between structures in subcortical/basal ganglia (putamen and thalamus) (Ystad, Eichele, Lundervold, & Lundervold, 2010), and reduced gray matter volumes in the basal ganglia are shown to be correlated with reduced performance on the first edition of the CVLT after cardiac arrest of various etiologies (Horstmann et al., 2010).

Wechsler Memory Scale-III (WMS-III)

The WMS-III 2002 is a battery of tests measuring learning, memory and working memory in the age spans 16-89 years with 11 subtasks. The WMS-III was co-normed with the WAIS-III and the combined factor index scores allows ability/memory comparisons (Mitrushina, Boone, Razani, & D'Elia, 2005). The Norwegian version of WMS-III was published in 2007 after controlling for the tests psychometric properties in Norwegians (Wechsler, 2007) and a later study confirmed that the Norwegian translation is psychometrically equal to the original WMS-III (Bosnes, Troland, & Torsheim, 2015). Two subtests were used in the Article 1 in the present study: The Digit span Test and the Spatial Span test. Both these tests are constructed to measure verbal and visual working memory, and reflects the ability to hold information in the phonological loop and the visuospatial sketch pad (Baddeley, 1992). Working memory tests, such as the Digit Span and the Spatial Span, are considered essential in neuropsychological examinations in order to differentiate working memory difficulties from long-term memory deficits (Strauss et al., 2006).

Rey Complex Figure

The Rey Complex Figure Tests (Meyers & Meyers, 2003) was originally developed in 1941 by Rey (Rey, 1941). It is extensively used in neuropsychological practice as a measure of visuospatial construction ability and visual memory. RCFT consists of 4 subtasks; copy, immediate memory, delayed memory and a recognition trial. All subtasks were administrated in the present study. The American original manual contains normative data from the age span 18-89 years of age. Small sample studies in Norwegian settings have shown good fit to the American normative data (Egeland et al., 2005). The RCFT is widely used both in clinical settings and research for assessment of visuospatial learning and memory (Strauss et al., 2006). The RCFT has been debated in terms of interrater reliability, and mixed findings exists, showing both high and low interrater-reliability estimates (Mitrushina et al., 2005). Improvements in scoring systems introduced after 2000 have probably increased interrater reliability (Deckersbach et al., 2000). Test-retest reliability is shown to be within the range of 0.65-0.80, and practice effects are reduced with longer test-retest intervals (Levine, Miller, Becker, Selnes, & Cohen, 2004). Practice effects are also dependent on demographic factors such as age and education that may elevate baseline scores, and thereby increasing practice effects (Levine et al., 2004). The RCFT is shown to be useful in predicting daily activities (Davies, Field, Andersen, & Pestell, 2011) that at least partly relies on visuospatial functioning, such as driving abilities (Marshall et al., 2007). The RCFT is sensitive to both dysfunctions in perceptual abilities (Ashton, Donders, & Hoffman, 2005) and reduced visual memory performance after traumatic brain injury (Strauss et al., 2006; Vanderploeg, Curtiss, & Belanger, 2005).

Delis Kaplan Executive Function System D-KEFS

The Delis Kaplan Executive Functioning System (D-KEFS) was developed as a co-normed battery of nine tests for assessment of several aspects of executive functions within the age span from 8 to 89 years (D. C. Delis, Kaplan, & Kramer, 2001), (D. C. Delis, Kramer, Kaplan, & Holdnack, 2004). The separate tests can be administrated individually or in groups. The D-KEFS battery is available in Norwegian with the normative data from the US standardization. Studies investigating psychometric reliability and validity measures have found that the D-KEFS have high psychometric quality, and the tests included are valid for examination of executive functions (Homack, Lee, & Riccio, 2005). To date, there are no studies that have investigated the psychometric qualities of the D-KEFS in Norwegian samples. We chose to assess aspects of executive functions with three separate tests from the D-KEFS. The following tests were administrated: Trail Making Test (TMT), Color-Word Interference Test and the Verbal Fluency Test. The D-KEFS' TMT measures rapid visual search, psychomotor speed and cognitive flexibility in a visuo-motor task. The Verbal fluency test measures verbal production and flexibility in a verbal task. The Color-word tests measures verbal inhibition. The D-KEFS' tests used in the present study are analogues to older and established tests that are included and normed in the Halstead-Reitan Neuropsychological battery (HRB) (Reitan & Wolfson, 1985). The D-KEFS versions have more sub-tasks than the original tests, i.e. the TMT has five separate tasks, whereas the original TMT has two. Thus, the inclusion of more detailed tasks give the opportunity to divide the test performance in separate parts such as processing speed, motor-speed, visual perception, which are requirements for completing the more complex executive tasks such as integration of the abovementioned functions measured in the original HRB tests. The D-KEFS test employed in the studies included in the present thesis are shown to be valid indicators of cerebral injury and pathology, however not superior to the original HRB-tests which several of the D-KEFS test are based on (Keifer & Tranel, 2013).

Grooved Pegboard (GP)

Motor functioning was assessed with the Grooved Pegboard Test for both hands in which each hand is summed and averaged. It has widespread use and reported sensitivity to cerebral dysfunction affecting cerebral motor-systems (Bryden & Roy, 2005; Mitrushina et al., 2005). Performance on the Grooved Pegboard is shown to be correlated with other measures of cognitive functioning such as executive functions, processing speed, memory and spatial organization, suggesting that the test demands more than simple psychomotor speed (Ashendorf, Vanderslice-Barr, & McCaffrey, 2009). The Grooved Pegboard has demonstrated good reliability and validity (Sureyya S Dikmen, Robert K Heaton, Igor Grant, & Nancy R Temkin, 1999). Because of the timed component, it is sensitive to cognitive slowing, sensitive to change across time and resistant to floor and ceiling effects (M. H. Lezak, D.B., Bigler, E.D. & Tranel, D. , 2012). Test-retest reliabilities have been reported to be in the range of approx. 0.80 (S. S. Dikmen, R. K. Heaton, I. Grant, & N. R. Temkin, 1999). Practice effects are generally reported to be small, but better performance is expected with several repeated assessments (Robert J McCaffrey, Duff, & Westervelt, 2000). The Grooved Pegboard is shown to be sensitive to several conditions resulting in diffuse brain dysfunction (M. H. Lezak, D.B., Bigler, E.D. & Tranel, D. , 2012), including cognitive deficits after coronary artery surgery with cardiopulmonary bypass (Nathan, Wells, Munson, & Wozny, 2001).

The Short Form (SF-) 36 questionnaire of Health Related Quality of Life

Health-related quality of life was measured with the Short Form Health 36-question survey form (SF-36) (J. E. Ware et al., 1994; J. E. Ware, Jr. & Sherbourne, 1992).

The SF-36 Norwegian version 1.2 was used (Loge & Kaasa, 1998). The SF-36 is a self-report questionnaire with 36 questions and among the most widely used generic and profile based measures of health related quality of life (Fayers & Machin, 2013). The questionnaire is designed to measure a person's perception of how their health status has interfered with their psychological, social and physical functioning for the previous four weeks and provides a measure of the relative burden of disease along 8 subscales where each represent a different dimension of health (Hann & Reeves, 2008). The respondent is asked to reply to questions on likert-type scales varying from 2-6 points.

The eight subscales are physical functioning (PF), physical role (RP), bodily pain (BP), general health (GH), mental health (MH), emotional role (RE), social function (SF) and vitality (VT) (J. E. Ware et al., 1994). Subscales can be averaged into two main scales, a physical component scale (PCS) and a mental component scale (MCS). These are calculated as the weighted sum of subscale scores (J. E. Ware, Jr. & Sherbourne, 1992). The scale range is 0-100 (worst-best). The online calculators for norm-based data scoring (http://www.sf36.org/nbscalc/index.shtlml) was applied for each survey in the present project, and the results are provided in normalized T-scores. When standardizing the scores according to the T-score distribution the means are 50 and the standard deviations are 10 across all summary scales and subscales on the SF-36 in the comparator group. Thus, a direct comparison between the participants' T-scores and the age- and gender-corrected normative data in the general Norwegian population can be viewed in a single graph and higher scores on all bars indicate better health related quality of life (Loge & Kaasa, 1998; J. E. Ware & Kosinski, 2001; Ware Jr, 2000).

Physical and mental health summary scores less than 40 (1 SD below the general population) indicate poor health (Andelic et al., 2010; McCarthy et al., 2006).

The normative Norwegian sample consist of 2323 persons, drawn from the general population. The age range of the normative sample was 19 to 80 years. Twenty-five percent of the sample reported past or current disease. The Norwegian normative data corresponds well with previous studies (Loge & Kaasa, 1998; J. E. Ware et al., 1994; J. E. Ware, Jr. & Sherbourne, 1992).

Hospital Anxiety and Depression Questionnaire (HADS)

The Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983) is a brief screening inventory for self-reported symptoms of anxiety and depression. The questionnaire has two subscales, one for depression and one for anxiety. Respondents are asked to fill out a 14 –item scale that consists of 7 questions for anxiety symptoms and 7 questions for depressive symptoms, respectively. Response options for each item range from 0 for no symptoms to 3 for the maximum number of symptoms. The score on each of the two subscales range from 0-21. Optimal cut-off points for the two subscales for identification of clinical significant cases of anxiety or depression have been evaluated to 8 (Bjelland, Dahl, Haug, & Neckelmann, 2002). The scale was originally developed to be used in non-psychiatric hospital clinics (Zigmond & Snaith, 1983). Therefore, all symptoms that are related to physical disorders, i.e. feeling fatigued or dizzy, were eliminated. The scale is validated in Norwegian with good psychometric qualities, (Mykletun, Stordal, & Dahl, 2001) and was currently psychometrically examined in a cardiac population (Årestedt, Israelsson, Herlitz, & Bremer, 2015). The scale is appropriate for a wide age span from youth to old age (Breeman, Cotton, Fielding, & Jones, 2015). The HADS has previously been extensively used in cardiac populations (Bambauer, Locke, Aupont, Mullan, & McLaughlin, 2005; Stafford, Berk, & Jackson, 2007) and after OHCA specifically (Lilja, Nilsson, et al., 2015; Schaaf et al., 2013).

Ethical considerations

The study was conducted in line with the principles outlined in the Declaration of Helsinki (WMA, 2013) and the principles in the Ethical guidelines for Nordic psychologists http://www.psykologforeningen.no/medlem/etikk/etiske-prinsipper-for-nordiske-psykologer (NPF, 1998).

The patients' well-being and integrity were put in front of the needs of the research or researchers. The patients who participated in these studies were at no risk; voluntariness was emphasized and confidentially was guaranteed. The protocol was reviewed and approved by The Regional Committee for medical research ethics in North Norway (REK 2009/1395) before the start of this study. However, in clinical research ethical considerations should be an ongoing process and not only considerations though upon before starting the project. Therefore, after some time gaining experience with the procedure, some practical adjustments were done and a new application was sent REK for approval.

The study was performed on the group that the results are to be generalized to (WMA, 2013). Leaving out the research, the OHCA survivors with more severe functional impairments was not viewed problematic as these patients are routinely taken care of in clinical practice at the hospital. However, survivors that were capable of neuropsychological assessment after 3 months, but not fulfilling all the inclusion criteria for research, were of ethical reasons, offered the assessment regardless of research participation. The benefits of the assessments were that if problems were identified and the patient gave consent, action was taken by health care personal to refer to existing services. All survivors were informed about recovery after OHCA and they all were given information about existing cardiac rehabilitation services. A copy of the neuropsychological report was sent to the patients' primary physician and the patient. The patient also got oral feedback from the results and could call the neuropsychologists if there was any questions after the assessment.

The benefits of research participation were viewed to outweigh potential harm (WMA, 2013). Burden or treats were viewed as minimal. However, generally some patients may experience stress and anxiety during a neuropsychological assessment or interview with a psychologist. Worth mentioning is also that the survivors were informed about the potential risk of OHCA causing brain-related problems from the cardiac ward, this was not new information provided at the time of follow-up assessment.

Although this research involved only adult people capable of giving informed consent, patients are a vulnerable group, and the requirements of giving understandable information and obtaining an informed consent was challenged by the fact that the research participants could have transient or permanent cognitive impairments, were in general reduced physical health, or were in high emotional distress. This can change the way information is received and remembered (Fields & Calvert, 2015). Further, the information about the procedure included some difficult information or words “cognitive” and “neuropsychological assessment” are not common words in everyday language. Special attention was therefore given to the procedure of obtaining informed consent and the way information was conveyed. First, information about the clinical follow-up was provided survivors from a specialist in rehabilitation medicine before hospital discharge from the cardiac ward. The doctor assessed the need for inpatient rehabilitation and also informed about the clinical service and mentioned the research project. The time of discharge was however not viewed as a good time to obtain informed consent to research. Survivors may still be confused, physically reduced, or feel pressured to say yes to research participation because the “hospital” just saved their life. The specialist in rehabilitation medicine registered the survivor in the rehabilitation ward as a possible research participant. Second, patients received a scheduled appointment for the assessment by mail, standardized information about the research project as provided by REK at the time with the consent form. As a third information, we chose to enclose an additional simplified note that briefly explained the rational for the clinical assessment, that the research project was optional and did not affect care provided by the hospital. Added to the letter was the telephone number to the health secretary organizing the scheduling and answering questions about the clinical assessment and the research project.

Additional comments on statistics and data analyses

The main hypotheses tested in the three studies were stated as assumptions of continuous linear associations between variables. Thus, the most appropriate framework for inferential statistics were the general linear model (GLM). The only analysis with non-parametric statistics were in Article III, where the non-normal frequency data was analyzed by the related samples McNemar's change test.

Multivariate GLMs were employed in Article I and III in order to assess the effects of demographic and disease-related variables on cognitive functioning. For the multivariate analyses, only significant univariate contrasts were reported along with measure of effect size. For the multiple linear regressions used in Article I and II, stepwise backwards entry of possible predictors in the analyses was chosen because some of the selected variables were tested in the absence of an a-priori hypothesis regarding the effect on neuropsychological variables (Field, 2013). In a backwards entry, all variables are entered, and then removed one by one after testing of contribution to the model. Furthermore, backwards regression methods was chosen due to the small sample size and risk of overfitting the models.

Multicollinearity is possible when assessing related constructs such as test scores from neuropsychological assessment (Field, 2013). However, when using the variance inflation factors (VIF) as a criterion for multicollinearity, there were no threats to the validity of the models (Article I & II) by multicollinearity when selecting a VIF-value < 2 as cut-off (O'brien, 2007).

Effect sizes were presented as η^2 (eta-squared) for the multivariate GLM in Article I, and R^2 for linear regressions in Article I and II. Hedges' *g* was calculated in order to display effect sizes of the change in continuous variables from 3 to 12 months post OHCA in study III. We chose Hedges *g* over Cohens *d* for this type of statistics because Hedges *g* adjust for sample size when estimating the effect size, which may be of special importance in small-sample studies (Field, 2013). Pearson correlations, *r*, were used to assess the correlation between normally distributed linear data. Furthermore, the Pearson *r* can also be viewed as a measure of effect size (explained variance), when the squared value of *r* is used (Field, 2013). However, even if the constructs measured in this thesis are theoretically related, *r*'s from simple correlations were not interpreted as effect measures. The use of *r* squared (R^2) was restricted to the linear regression analyses where more than two varibles were compared simultaneously.

Standardisation of scores to a common metric

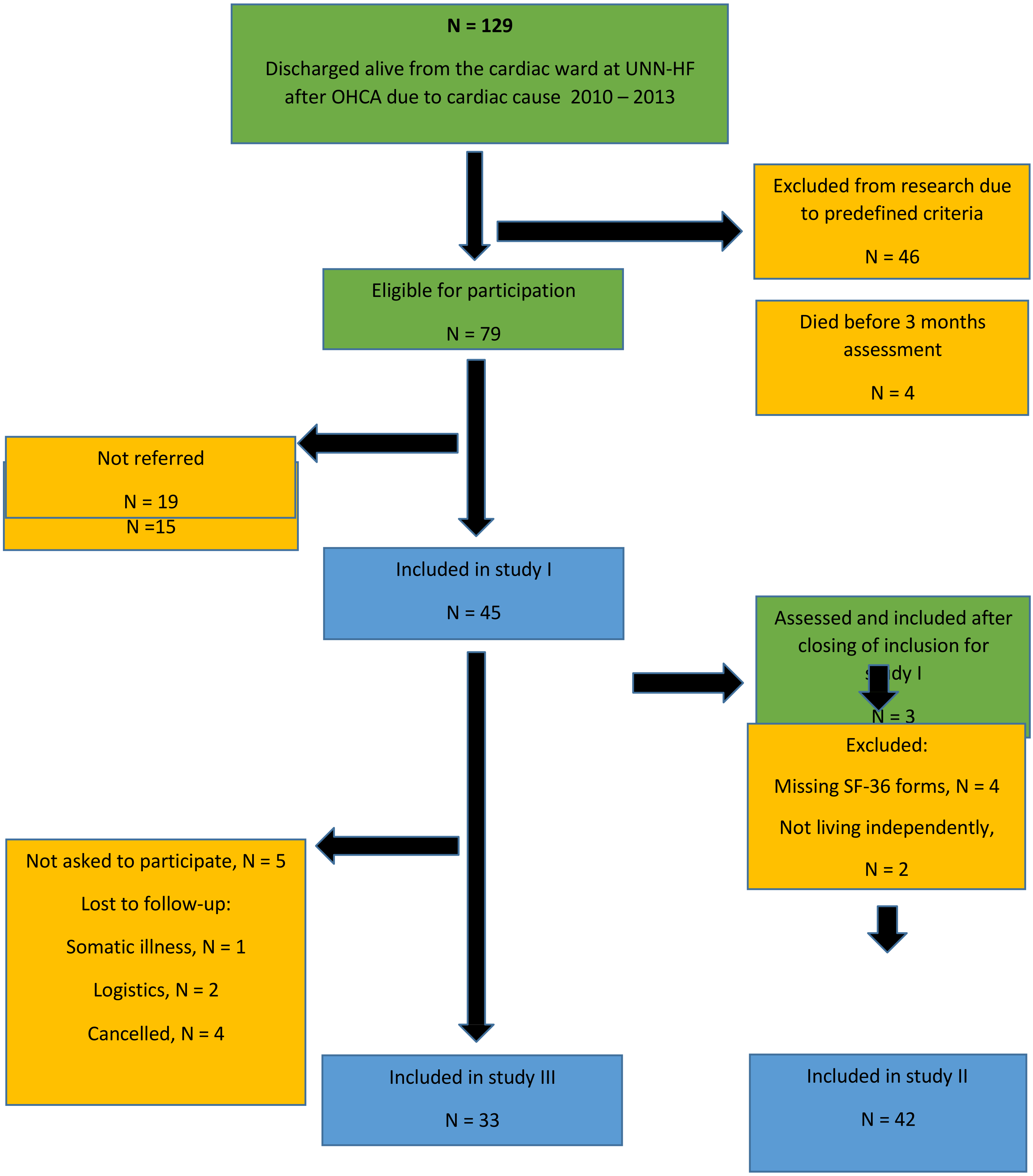
Because the neuropsychological tests are standardised by different scales (T-scores (mean 50, SD 10), Wechsler Scales scores (mean 10, SD 3), Z-score transformations were calculated in order to allow direct comparison of results across tests. The formula used for this transformation is straightforward: $Z = \frac{x-\mu}{\sigma}$ where x is the test score of the single patient, μ is the normative mean from the norms of each test, and σ is the standard deviation of the normative mean.

Summary of Article I-III

Participants in study I-III

Figure 1 gives an overview of the total cohort of OHCA survivors, all from a presumed cardiac cause, identified as discharged alive from the cardiac ward in the study period. Numbers for excluded survivors, loss to follow-up and unwillingness to participate are given. According to electronic hospital records there were 197 patients discharged from the cardiac ward after OHCA of any cause (ICD-diagnosis of I46.0: Cardiac arrest with successful resuscitation or I46.9: cardiac arrest unspecified) in the period of data collection. 129 of these were from a cardiac cause or presumed cardiac origin. In Figure 1, it is shown that 79 OHCA survivors were eligible of participation at 3 months follow-up. The exact details on inclusion, exclusion and loss-to follow up are provided in each of the Articles I-III. Totally 48 (61%) of the eligible survivors were included in the data analyses across the three articles.

Figure 1. Overview of participants in Article I-III from the initial cohort identified



Article I

Ørbo M, Aslaksen PM, Larsby K, Norli L, Schäfer C, Tande PM, Vangberg TR, Anke A.
Determinants of cognitive outcome in survivors of out-of-hospital cardiac arrest.
Resuscitation. 2014 Nov;85(11):1462-8.

Aims: The aims of the study were to assess if demographic, medical or resuscitation characteristics could account for variance in cognitive performance 3 months after successful resuscitation and identify cognitive impairment.
Hypotheses: We expected longer coma duration to be associated with poorer cognitive test results. We expected tests of memory, attention and executive functions to show significant impairments (V. R. Moulaert et al., 2009).
Results: Forty-five survivors (4 women), mean age was 60.4 (SD 12.4) were included. The OHCA characteristics of the survivors were similar in the way that all but one had a witness OHCA, by-stander resuscitation was initiated in all but one participant, all but one had a shockable rhythm as first registered on the scoop. However, time to ROSC was highly variable (1- 60 minutes, mean 17.6 minutes) as was coma duration (2 minutes – 192 hours, mean 39.9 hours). Thirteen patients were awake at admission.

At 3 months, all but two were living independently or with a spouse. The performance on the different neuropsychological tests were presented as the average performance across the subtests that belongs to a certain test. Tests with different normative data were not mixed. The mean scores of the CVLT-2, Color-Word from the D-KEFS and the Grooved Pegboard test were significantly below normative means. When impairment was set to T = < -1.5 SD from the normative mean, 56% of the participants had all the averaged tests scores above the cut-off for impairment. The frequency of impairment on the cognitive tests ranged from 9 to 31%. HADS scores were generally low indicating absence of clinical symptoms of anxiety or depression. Only five (11%) scored above the cut-off on the anxiety subscale on the HADS, none on the depression subscale.

Shorter coma duration and induced hypothermia treatment were associated with favorable cognitive outcomes. These two variables explained 45% of the variability in the global cognitive composite score in a general linear model where covariates were age, years of education, coma duration (in hours), time to return of spontaneous circulation (ROSC) and factors were pervious cardiac disease (yes/no) and hypothermia treatment (yes/no). Coma duration was predictive across all cognitive tests, hypothermia treatment of specific tests of memory (CVLT-2), attention and executive functioning (the Color-Word test from D-KEFS).

Conclusions: The main finding is that coma duration predicted cognitive outcome severity. This has been regularly suggested in the literature, but is not much empirically explored with neuropsychological tests of cognition as outcome measure in long-term survivors where most have resuscitation characteristics associated with a favorable prognosis (Lim & Alexander, 2010). The pattern of cognitive impairments most frequently found fit to previous reports. However, the frequency of cognitive impairments and emotional problems were lower compared to some previous reports, which may be due to differences in sample characteristics or operationalization of cognitive impairment and cognitive domains (Alexander et al., 2011; V. R. Moulaert et al., 2009).

Article II

Ørbo M, Aslaksen PM, Larsby K, Schäfer C, Tande PM, Vangberg TR, Anke A.

Relevance of cognition to health related quality of life after survival from out-of-hospital cardiac arrest. Journal of Rehabilitation Medicine 2015;47(9): 860-866.

Aim: The aim was to explore if and how neuropsychological tests of cognitive domains previously reported as frequently impaired after OHCA; Memory-, executive- and psychomotor functioning, are related to the physical and mental aspects of HRQL. HRQL was measured with the SF-36 three months post OHCA. We expected poorer memory scores to relate to poorer results on the SF-36.

Results: 42 survivors (mean age = 62.4 , SD = 11.38, 4 were women) were included fitting to our definition of a good outcome survivor. This was defined as being functionally independent and community dwelling two months post arrest, discharged directly to own home from the cardiac ward receiving no organized care. None of them reported depressive symptoms on the HADS above cut-off indicating absence of depression. Thirty-nine were living with a spouse. Half of them (N=21) were retired before OHCA. Of the 21 that were active workers before OHCA only 3 had returned to work after 3 months.

Significant associations were found between cognitive domains and SF-36 reports 3 months post resuscitation. The regression analyses showed that worse performance on tests of psychomotor functioning was associated with worse scores on the main physical component on the SF-36. Worse memory test performance was associated with worse scores on the mental SF-36 component. Coma duration, age or years of education was not significant contributors in the regression models. The neuropsychological tests showed impairments most often in the memory domain. 30% of the survivors were impaired on tests for recall memory. Not all impairments were mild.

The mental component of SF-36 was above T = 40 in 80%, comparable to healthy normative controls. 60% reported a physical HRQL in the normal range (Andelic et al., 2010; McCarthy et al., 2006). The mean physical component of the SF-36, but not the mean mental component of the SF-36 was significantly worse than Norwegian population data. The subscales on the SF-36 physical component that was significantly reduced was the General Health subscale and the Physical Role functioning subscale. On the mental component on the SF-36, the Emotional Role subscale was significantly below the normative mean.

Conclusions: The results suggest that the cognitive impairments frequently reported to occur in survivors with so-called good outcomes may cause disability and need intervention to enhance health related quality of life. Thus, good outcome survivors should be screened for cognitive impairments after OHCA.

Article III

Ørbo M, Aslaksen PM, Larsby K, Schäfer C, Tande PM, Anke A.

Does cognitive outcome change from 3-12 months in survivors from out-of-hospital cardiac arrest? Submitted September 2015.

Aims: 1) To investigate if cognitive functioning change from three to twelve months after resuscitation. 2) To assess if cognitive impairment detected at 3 months after OHCA is related to reduce HRQL, emotional problems or work status after 12 months.

Results: Of the 40 survivors from Article I invited to repeated assessment, 33 (82.5%) completed both assessments (31 males, mean age 58.6 SD = 13). All lived independently at 12 months. We found no difference in the following variables for the participants tested only at 3 months compared to patients tested at both 3 and 12 months: 3 month averaged neuropsychological tests scores, demographic variables, medical, resuscitation or treatment characteristics.

Assessment of cognitive change: Statistical significant, positive cognitive change was found from 3-12 months in tests of visual memory (Rey Complex Figure Test), executive function (Trail Making Test 4, Word-Fluency Test 4; D-KEFS) and in the mean of cognitive composite scores across domains. Effect sizes were small (Hedges g </= .26). Statistical change was not significant for the verbal memory composite score (California Verbal Learning Test-II), psychomotor composite (Trail Making Test 5; D-KEFS, Grooved Pegboard) or general intellectual function (Wechsler Abbreviated Scale of Intelligence). Demographic variables associated with statistical significant cognitive change were younger age and longer education.

When dividing the participants according to the presence or absence of cognitive impairment at 3 months and then assessing the magnitude of change for each group. The results showed that the group of participants with impairments detected at 3 months (N = 11), still had a statistical significant change, while the participants without impairment at 3 months did not display significant change.

Association between cognitive impairment at 3 months and HRQL and work status at 12 months: Lower scores on at the mean cognitive composite across cognitive domains from 3 months was correlated with lowered scores in the main physical component of the SF-36 at 12 months. No improvements were observed on the SF-36 from 3 to 12 months post-arrest. The physical component did not change. The mental SF-36 component was significantly reduced from 3-12 months indicating more limitations in daily activities due to emotional problems. HADS scores at both 3 and 12 months were generally low. There was a statistical increase in total HADS scores from 3-12 months, still only 2 participants reported HADS scores above the cut off for clinical significant symptom level at 12 months. A significant increase in work participation was observed from 3 to 12 months. Of the eighteen survivors employed before OHCA, two were returned to work after 3 months and eleven after 12 months. Only one of the participants scoring in the impaired range at 3 months had returned to work at 12 months.

Conclusions: Although some scores show significant positive change, the overall results suggest little average improvements, keeping it open whether clinical meaningful change can occur in some survivors and over longer time delays than one-year post arrest. By far however, early testing seem to presage longer-term outcomes and this is supported by one other recent study (Lim et al., 2014). We suggest that cognitive impairments detected early after OHCA (at least 3 months after) can determine who is in need of follow-up.

Supplementary discussion

Cognitive impairments are common after out-of-hospital cardiac arrest (OHCA)

The majority of the survivors assessed in the present project had no cognitive impairments detected on neuropsychological tests at 3 months after OHCA and did not report affective symptoms above critical cut-off points on the Hospital Anxiety and Depression Scale (HADS) (Bjelland et al., 2002; Herrmann, 1997; Orbo, Aslaksen, Anke, & T., 2015; Orbo et al., 2014; Orbo, Aslaksen, Larsby, et al., 2015; Schaaf et al., 2013; Zigmond & Snaith, 1983). The results of other prospective studies using similar outcome measures have come to the same conclusion; OHCA of cardiac cause with initial shockable rhythm presented and early initiated by-stander resuscitation is frequently compatible with no, or only mild cognitive impairments and with the absence of symptoms on anxiety or depression (Alexander et al., 2011; Anderson & Arciniegas, 2010; Cronberg et al., 2009; Lilja, Nielsen, et al., 2015; Sauve, Walker, et al., 1996; Tiainen et al., 2007; Tiainen et al., 2015; van Alem et al., 2004).

The present study cannot correctly inform correctly about prevalence estimates for cognitive impairments or HADS results after OHCA. The reasons for this inability are the small sample and the selection bias toward survivors with more characteristics associated with fortunate prognosis (Goossens & Moulaert, 2014).

The largest (n= 287) prospective multicenter randomized control trial (RCT) of cognitive outcomes (Lilja, Nielsen, et al., 2015) after cardiac-caused shockable rhythm OHCA was published recently. The size of this study implies reliable estimates of the prevalence of cognitive deficits in the OHCA population. The main aim of this trial was to compare cognitive outcomes of survivors treated with temperature management regimes of 33°C or 36°C, and no group difference was found. However, in the full sample, more than 50% of survivors were cognitively impaired 6 months after resuscitation (Lilja, Nielsen, et al., 2015). Another recent prospective study with neuropsychological testing 6 months after OHCA (Tiainen et al., 2015) summarize; despite the last decades advancements in resuscitation and medical care that produce more survivors with good CPC scores (Cronberg et al., 2015; Tiainen et al., 2015), mild and moderate cognitive problems are still frequent in long-term survivors.

Despite the selection bias towards survivors with favorable outcome characteristics in the present study and the inability to provide correct prevalence rates, it is evident from the results that neuropsychological tests rather frequently detected cognitive impairment in several cognitive domains (Orbo et al., 2014; Orbo, Aslaksen, Larsby, et al., 2015). Even in Article II, where the inclusion criteria were slightly stricter, 30% of the participants showed significant impairments in delayed verbal recall memory, and not all impairments were mild. Improvements in cognitive impairment were very limited for those re-assessed at 12 months. Lower cognitive functioning was associated with having poorer HRQL and not returning to work. Overall, the results from the present study support previous claims: persistent cognitive impairments of various types and severity may frequently go undetected in clinical care because they are not unequivocally addressed at follow-ups visits after OHCA (N. R. Grubb et al., 1996; V. R. Moulaert et al., 2015).

The participants in the present study were carefully selected based on their premorbid good functioning and the exclusion of comorbid disorders. This increased the probability that the cognitive impairments observed were due to OHCA-related brain injury and that few other risk factors were involved (Orbo et al., 2014; van Alem et al., 2004). In addition, the low HADS scores suggest that cognitive impairments were less likely due to affective problems. The selective inclusion criteria also limit the generalizability of the results to the wider OHCA population.

Affective symptoms

Lilja et al (2015) also reported HADS scores in the above-mentioned RCT trial (n=278). Six months after OHCA, 24% had elevated anxiety, and 13% had elevated symptoms of depression (Lilja, Nilsson, et al., 2015). In the present study, elevated symptoms of anxiety were found in 11% of the participants, but elevated depressive symptoms were found in none of the survivors assessed at 3 months. The HADS scores in the present study were also lower than in some other reports using HADS (Schaaf et al., 2013). Survivors with affective disorders diagnosed prior to OHCA were excluded from the present study (Davydow, Gifford, Desai, Needham, & Bienvenu, 2008). It is speculative, but perhaps relevant, that very few of the survivors assessed in our study had returned to work and the majority lived together with a spouse. Low environmental demands may have caused less emotional distress in the survivors with cognitive impairments. If some survivors lacked awareness of their cognitive deficits or if the cognitive impairments in some survivors were too mild to cause emotional concern are relevant but unanswered questions. Moreover, fewer survivors in our study compared with those in the study by Lilja et al (2015) had cognitive impairments.

Several cognitive functions are at risk after OHCA

On the neuropsychological tests in Article I, significant mean differences between survivors and normative data were found on three tests: the CVLT-II, the Stroop Color Word and the Grooved Pegboard. This patterns of cognitive impairment with a relative vulnerability found in aspects of memory (CVLT-II), attention/executive functions (Stroop C-W) and finemotor/psychomotor functions (GP) supports previous findings (Alexander et al., 2011; Anderson & Arciniegas, 2010; Lim et al., 2004; B. A. Wilson, 1996). The frequency distributions for each of the tests (Table 3 in Article I) show that impairments in cognitive functions were not isolated to these three tests. The most frequently affected test was the Rey Complex Figure Test, for which the average score across subtests were at or more than 1.5 SD below the normative mean in 30% of survivors. The RCFT mainly measures visuospatial ability and brief and delayed memory for a complex figure (Meyers & Meyers, 2003). Multiple cognitive domains are at risk after OHCA and range in severity from only mild to more severe (Alexander et al., 2011; Anderson & Arciniegas, 2010; Lim et al., 2004; B. A. Wilson, 1996).

The 2011 guidelines for primary outcomes in resuscitation science studies recommend the inclusion of at least one neuropsychological test for attention, memory and executive functions should be included (L. B. Becker et al., 2011). However, this may indicate that one neuropsychological test is a pure measure of one function. Although one neuropsychological test or subtest is designed to measure one specific function, it actually measures overlapping functions (Duff, Schoenberg, Scott, & Adams, 2005; M. H. Lezak, D.B., Bigler, E.D. & Tranel, D. , 2012; Miyake & Friedman, 2012; Miyake et al., 2000). Thus, a poor result on one test may be caused by problems with functions other that the problem it is designed to measure. Problems with executive functions may also manifest as problems on many tests that are not necessarily intended to measure a specific executive function (R. C. Chan, Shum, Toulopoulou, & Chen, 2008; Duff et al., 2005; Lim & Alexander, 2010). For instance, the CVLT-II shows impaired performance in patients with damage to the frontal lobes (Alexander et al., 2003). Each neuropsychological tests can be regarded as mainly representative of one function, but the tests are not pure measures of one function (Miyake & Friedman, 2012; Miyake et al., 2000). Furthermore, the clinical tests are not developed to measure discrete functions of the brain (Miyake & Friedman, 2012; Miyake et al., 2000). This shows the importance of including a variety of tests and research designs in studies of cognition after OHCA (Haatveit et al., 2015; Miyake et al., 2000).

Longer coma duration is associated with poorer cognitive outcome

Longer coma duration and lack of hypothermia treatment was associated with poorer cognitive functioning at 3 months. The relationship between coma and hypothermia cannot be separated in our study, and no conclusions about the potential neuroprotective effect of hypothermia can be drawn (Goossens & Moulaert, 2014; Jepsen, Johnsen, Gillman, & Sorensen, 2004; Orbo et al., 2014). When this study was conducted, hypothermia was a standard treatment for patients who did not regain consciousness after ROSC and was therefore considered relevant to include in the statistical models. Hypothermia treatment was associated with better cognitive results, specifically in one tests for verbal learning and memory and in one test for executive functioning. The two RCT trials conducted have not found support for lower rates of cognitive impairment in hypothermia-treated survivors compared with those who did not receive hypothermia treatment or those who received regular temperature management (Lilja, Nielsen, et al., 2015; Tiainen et al., 2007).

It has previously been suggested that discrepancies in the information reported on the frequency and severity of cognitive impairments after OHCA can be partly explained by the failure to control for the coma duration of the participants in those studies. The present results support this conclusion (Alexander et al., 2011; Lim & Alexander, 2010; Lim et al., 2014). The frequencies of cognitive impairments reported in the present study may also be lower because survivors who awakened soon after resuscitation were not excluded. It remains to be empirically verified whether coma-duration has a definite cut-off point for cognitive dysfunction.

Future research on the predictors of mild and moderate cognitive impairment could result in knowledge useful for identification of survivors in need of further follow-up earlier and more efficiently (Aiyagari & Diringer, 2015; Orbo et al., 2014; Tiainen et al., 2015). Risk factors for cognitive impairment in OHCA survivors are assumed to be multiple, and study samples of sufficient size could address the relative contribution of factors related to cardiovascular disease, intensive care unit-related factors or other comorbidities for cognitive outcomes on neuropsychological tests (Aiyagari & Diringer, 2015; Arawwawala & Brett, 2007; Cronberg et al., 2015).

OHCA related cognitive impairment may cause disability

The significant associations found between the HRQL questionnaire and neuropsychological tests of cognition from the second article have face validity. It is easy to imagine that problems with remembering new information may interfere with performing social roles or cause emotional distress and that slower speed in the performance of several tasks in daily life is problematic.

The neuropsychological tests of executive functions did not exhibit a significant association with the SF-36 survey in Article II (Orbo, Aslaksen, Larsby, et al., 2015). The D-KEFS tests selected to represent executive functions did show a lower frequency of impairment relative to the memory tests. Tiainen et al (2007) found executive tests to be more frequently impaired than tests for memory. In addition, when controlling for age and education, Lilja and colleagues (Lilja, Nielsen, et al., 2015) found that tests of attention and executive functions better discriminated between OHCA survivors and cardiac controls than did a memory test. Our sample in Article II consisted of more survivors with shorter coma duration, without cognitive impairments and probably with milder impairments than the survivors considered in the studies by Lilja et al (2015) and Tiainen et al (2007).

The selected subtests of executive functions (Stroop inhibition, TMT switching) measures only a few aspects of executive functions. Executive functions may have limited representation through the tests selected (R. C. Chan et al., 2008; Chaytor, Schmitter-Edgecombe, & Burr, 2006; M. H. Lezak, D.B., Bigler, E.D. & Tranel, D. , 2012). Other aspects of executive functioning such as personality changes, changes in behavioral regulation and mood or lack of drive/motivation were not measured in the present study. Such changes are reported to occur rather frequently after hypoxic-ischemic brain injury and may be highly relevant to success in everyday activities and social participation (Anderson & Arciniegas, 2010; Caine & Watson, 2000; R. C. Chan et al., 2008; Chaytor et al., 2006; Lim & Alexander, 2010).

Notably, there was a low degree of explained variance in our models assessing the association between cognitive domains and HRQL. However, few variables could influence HRQL were included in the models, and the majority of survivors in the present study did not have cognitive impairments (Orbo, Aslaksen, Larsby, et al., 2015). The optimal variables to include and combine in models of HRQL after OHCA are not clear (Arawwawala & Brett, 2007; V. R. Moulaert et al., 2010). It is suggested that after traumatic brain injury (TBI), HRQL should be measured with both generic- and disease specific questionnaires, as well with methods that specifically address cognitive impairments and disability (Polinder et al., 2015). After cerebral stroke, it is suggested that neuropsychological tests of cognition are so strongly associated with quality of life that they could act as surrogate markers for quality of life questionnaires in the early stage after stroke (Cumming, Brodtmann, Darby, & Bernhardt, 2014). Cognitive impairments occur at a high rate after OHCA according to recent, large well-controlled studies, and it seems relevant for future studies to further address the relevance of cognitive and other psychological variables to HRQL. Similar studies of analyses between neuropsychological variables and HRQL questionnaires are published for other groups with frequent cognitive impairments (Boosman et al., 2015; Cumming et al., 2014; Hochstenbach et al., 2001).

Significant associations between traditional neuropsychological tests for cognition and generic HRQL questionnaires are explored in one other study after OHCA (Lim et al., 2014). Significant associations between worse performance in all neuropsychological domains and worse reports on the Sickness Impact Profile (SIP) were found 12 months post-arrest. In this study of 25 survivors, all had cognitive impairments, and all received rehabilitative care. SIP scores were significantly lowered for OHCA survivors compared with a control group with acute coronary syndrome.

Cognitive impairments should be detected early after OHCA and resuscitation

As expected, little cognitive recovery was observed in the scores on neuropsychological tests for cognition when re-assessed at approximately 12 months post-resuscitation (Lim & Alexander, 2010; Lim et al., 2004; Lim et al., 2014; Orbo, Aslaksen, Anke, et al., 2015; Roine et al., 1993; Sauve, Walker, et al., 1996). As suggested in Article III, studies of cognition using neuropsychological tests after OHCA would obtain similar results regardless of the time point chosen between 3 and 12 months. The results pertaining to cognitive change from 3-12 months require an additional comment on statistical versus clinical significance on an individual level. Showing (minor) statistical change at the group level does not equal recovery or deterioration at an individual level (Bowden, Harrison, & Loring, 2014; Philip D Harvey & Keefe, 2015). In clinical care, it would be relevant to know the characteristics associated with improvement potential. More information about clinically significant cognitive change on an individual level might have been achieved in our third article if the study had included a reliable change index or a more consensus-based definition a nonrandom change at an individual level, i.e., 1 SD (Duff, 2012; Philip D Harvey & Keefe, 2015; Heilbronner et al., 2010). Currently, little is known about individual characteristics associated with the greater potential for recovery from cognitive impairments after OHCA (V. R. Moulaert et al., 2009). It is, however, likely that recovery is not homogenous across all patients and that some may have greater recovery potential with rehabilitation interventions than others (Millis et al., 2001). Cognitive recovery after traumatic brain injury has been studied more than cognitive recovery after OHCA. It has been shown that subgroups and individuals exhibit delayed improvement or decline over time (R. J. McCaffrey & Westervelt, 1995; Millis et al., 2001) Research on even longer-term outcomes, beyond the first year after resuscitation, seems interesting, as recent studies show a long life expectancy for subgroups of OHCA survivors (Harve et al., 2007; Lindner et al., 2014; V. Moulaert, 2014).

Also observed in our third article was a statistically significant change in the main mental component of the SF-36 from 3 to 12 months. The component showed a decrease together with an increase in HADS scores, which is indicative of more emotional problems over time. However, all values for Hedges *g* as a measure of effect size for the change from 3 to 12 months were below the recommended cut-off point of .41 for a “practical” significant effect (Ferguson, 2009). It is known that different time points for outcome measurement may produce different results (Larsson et al., 2014; V. R. Moulaert et al., 2010; Raina et al., 2015; K. Smith, Andrew, Lijovic, Nehme, & Bernard, 2015). The concern has been raised that measuring HRQL too early may underestimate the possible range of functional recovery

(Raina et al., 2015; K. Smith et al., 2015). The sample size and effect sizes in the present study makes specific conclusions uncertain, but generally it is also possible to assume the contrary; cognitive impairments and emotional problems may hinder general functional improvements, prevent return to work and result in increasing disability over time in the absence of interventions. Thus, if cognitive impairment significantly hinders successful functional recovery and good HRQL, then cognitive impairment should be detected early after resuscitation, so that interventions aimed at improving HRQL in cognitive impaired survivors can be initiated (Elliott et al., 2011; Hochstenbach et al., 2001; Lim et al., 2014; V. R. Moulaert et al., 2015; V. R. Moulaert et al., 2010; Passier, Visser-Meily, Rinkel, Lindeman, & Post, 2013).

Additional methodological considerations

One shortcoming of the data is that we relied solely on secondary markers of the severity of brain injury only, such as coma length and cognitive tests. Supplementary MRI data might have improved our results allowing us to more confidently conclude that cognitive impairments were due to cerebral pathology and hypoxic-ischemic pathology specifically. Without reliable observations of brain damage, the etiology of cognitive impairments in OHCA survivors remains ambiguous. Standard clinical MRI could have eliminated other pathological reasons for the cognitive impairments observed and shown the degree and localization of ischemic lesions in grey and white matter (Sulzgruber et al., 2015). More advanced MRI protocols allowing volumetric loss in grey and white matter to be displayed and correlated with cognitive test results could increase understanding of the correlates between the brain and cognitive functions and plasticity potential resulting from spontaneous recovery or treatment (Fischl, 2012; Park & Friston, 2013).

The validity of the present results could have been improved with the use of co-normed tests for various cognitive functions and normative data for repeated testing.

When comparing the frequencies of impairments on the same test between Article I and II (see Table 3 in Article I and Table 2 in Article II), one can observe that some nuanced descriptive information about impaired and spared cognitive sub-functions from a specific test was lost when averaging all subtests into a common score, as done in Article I. All the neuropsychological measures include several sub-measures, which may not be equally affected by OHCA. Averaging subtest scores that measures different aspects of a cognitive function in the first article may contribute to underestimating cognitive impairments, as all standardized subtests scores contributed equally to the total score. For instance, the average scores across all CVLT-II subtests in Article I was described as below -1.5 SD in only 13.3% of participants. In Article II, only the CVLT-II sub-scores of short and long-delayed recall was considered. When the cut-offs for impairment were kept the same, 33% of the survivors scored in the impaired range on the sub-test of long-delayed recall. This increase in delayed recall memory impairments from Article I to II, occurred even though the survivors with the poorest outcomes were excluded. This result shows that the operationalization and statistical approaches to the analyses of cognitive impairment may produce different results in impairment rates even on the same test (Jackson, Gordon, Ely, Burger, & Hopkins, 2004; M. S. J. Schoenberg, 2011; van Dijk et al., 2000).

There are also shortcomings of the choice of secondary outcome variables. Independent living was registered both when patients lived alone and when they lived with a spouse. Including a measure of independence in instrumental daily activities as reported by both the spouse and patients could have contributed important information. It is unclear to what degree the survivors depended on their spouse for independent living or whether the survivors were succeeding with independent living (R. C. Chan et al., 2008).

Rates of return to work were shown to be very low for people with cognitive impairments detected at 3 months in our study. High rates of return to work have been shown in other larger studies of OHCA (Kragholm et al., 2015). Although return to work is an important measure of participation, it should be acknowledged that there are many personal and environmental factors that influence not to return to work in addition to cognitive functioning (R. C. Chan et al., 2008).

The HADS is only a very brief screening tool for anxiety and depression symptoms. Other emotional concerns after OHCA may be equally relevant, and other instrument may detect different problems (Schaaf et al., 2013). Even more relevant for future studies, according to recent publications, is the inclusion of measures of care-givers' emotions following OHCA. Moulaert et al (2015) showed that HADS scores were more elevated in caregivers than in survivors during the first year after cardiac arrest. The observation is important, not only because caregivers should be given support but also because their stress may impact the recovery path for survivors (van Heugten, Visser-Meily, Post, & Lindeman, 2006). The importance of including caregiver observations in evaluation of cognitive functioning after OHCA has been shown previously (Lilja, Nielsen, et al., 2015; Lilja et al., 2013; V. R. Moulaert et al., 2015; Pusswald et al., 2000).

As discussed in the third article, practice effects are a major concern in repeated neuropsychological assessment. Disease-matched control groups with similar age, demographic and gender characterizations can be used to better disentangle real improvement from practice effects (Heilbronner et al., 2010; Lim et al., 2014). However, practice effects are not equal between persons or groups (Heilbronner et al., 2010; R. J. McCaffrey & Westervelt, 1995), which may be a problem in studies with small samples as in the present research. Normative data were assumed to be better for comparison than a small control group with the risk of inducing more random heterogeneity. Furthermore, in the absence of ceiling effects, practice effects are preferred over sparsely correlated alternative measures, which would prevent the identification of improvement (Philip D Harvey & Keefe, 2015).

Clinical implications

Resuscitate the heart and remember the brain

Permanent cognitive impairments are a real concern, even in those survivors who are capable of independent living soon after hospital discharge. When survivors are not candidates for inpatients rehabilitation, mild and moderate cognitive impairments may go unrecognized if not systematically assessed. Providing follow-up assessments at some point after discharge that include cognitive assessment, will help identify survivors in need of tailored care and treatment. There is limited research to support specific optimal time points or cognitive tests, but recent consensus-based guidelines have been published (Nolan et al., 2015).

The battery of neuropsychological tests administrated in the present study was too demanding for some patients, and a briefer battery of tests would have been more feasible. In addition, many OHCA survivors do not have cognitive impairments, and a lengthy test session for all survivors seems unnecessary with regard to the demands placed on them. The selected tests in the current study are not eligible as a screening model for cognitive outcomes after OHCA, and they were never intended to constitute such a model. A more stepped approach to cognitive assessment is viewed as more sensible in clinical practice (Goossens & Moulaert, 2014; Nolan et al., 2015). Nevertheless, it is not entirely clear what precise results from an initial cognitive screening procedure should warrant referral to further assessment of cognition. More fine-grained knowledge of impaired and spared cognitive functions as well as the severity of the impairments, which is obtained by neuropsychological assessment, are sometimes necessary to allocate and initiate care and treatment tailored to meet the specific needs of the individual.

When cognitive impairments or emotional problems are detected at follow-up, it is reasonable to assume that existing treatment approaches can be both applicable and effective (V. Moulaert, 2014; V. R. Moulaert et al., 2014; V. R. Moulaert et al., 2015; Nolan et al., 2015). There are evidence-based approaches for improving quality of life for persons with cognitive deficits in memory or executive functions. The realistic goal may not necessarily be normalization of cognitive functioning, but optimizing functioning in everyday life may be more reasonable (F. Becker, Kirmess, Tornås, & Løvstad, 2013; Cappa et al., 2005; Cicerone et al., 2011; B. A. Wilson, 2013). Physical activity also improves cognitive functioning (Wilcox et al., 2013), and physical activity is an important part of cardiac rehabilitation programs aimed at increasing physical activity capacity and perceived physical health (Gordon et al., 2004). It is uncertain to what extent OHCA survivors attend cardiac rehabilitation programs (Boyce-van der Wal et al., 2015). Treatment of anxiety and depression in cardiac patient has been shown critically important for both mental and physical health (N. Frasure-Smith, Lesperance, & Talajic, 1993). There are well-known treatment options for emotional problems such as anxiety and depressive disorders (V. R. Moulaert et al., 2015)**.** Previous psychosocial interventions in cardiac patients have shown beneficial health effects (Linden, Stossel, & Maurice, 1996). The results of a recent RCT trial showed significant effects of a brief intervention with a nurse 3 months after cardiac arrest in terms of reduced anxiety symptoms and increased likelihood of return to work 12 months after cardiac arrest (V. Moulaert, 2014; V. R. Moulaert et al., 2014; V. R. Moulaert et al., 2015).

The present thesis focused on cognitive impairments. Several other psychological and medical problems in addition to cognition may be relevant to address systematically at follow-up consultations after OHCA. Cognitive problems do not exist in isolation, and multiple problems may be relevant from a patient-centered perspective (Arawwawala & Brett, 2007; Dougherty, 1994; V. R. Moulaert et al., 2015; Nolan et al., 2015).

Conclusions

In the present study, it was concluded that longer coma duration was associated with poorer cognitive functioning 3 months after successful resuscitation from OHCA. Memory, executive- and psychomotor functioning were significantly impaired. Poorer cognitive results on tests for memory and psychomotor functioning were associated with perceived disability. Little change was detected in the outcome measures used from 3 to 12 months. The strenghts of the present study are its prospective design, the inclusion of surviors with a similar etiology of cardiac arrest and two time points used for follow-up assessment. The main limitations the are small sample size, an observational design without controls, loss to follow-up and selection bias, which limits generalizability. The main results are generally consistent with larger and more well-controlled studies. To some extent, the studies generates slightly new suggestions that may be worthy of further investigation.

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Appendix

Table: Overview of cognitive tests and composite scores in the three articles.

	Study 1	Study 2		Study 3	
Test used	Subtest	Subtests	Composite	Subtests	Composite
Wechsler Adult Scale of Intelligence (WASI) General cognitive abilities (IQ)	Matrix reasoning, Block design, Vocabulary, Similarities	Matrix reasoning and Vocabulary	General cognitive ability	Matrix reasoning and Vocabulary	General cognitive ability
California Verbal Learning Test-2 (CVLT-2) Verbal learning and memory	Learning trials (1-5), memory interference, short and long delay recall (free and cued), long-term recognition	Free short and long delay recall	Verbal memory	Free short and long delay recall	Verbal memory
Rey Complex Figure Test (RCFT) Visuo-spatial and visual memory	Copy, immediate recall, delayed recall and visual recognition	Immediate recall, delayed recall	Visual memory	Immediate recall, delayed recall	Visual memory
Wechsler Memory Scale-3 (WMS-3) Memory span	Digit- and spatial span, forwards and backwards.				
Delis-Kaplan Executive Function System (D-KEFS) Executive functioning	Trail-Making Test (1-5), Color-Word Interference Test (1-4), Verbal Fluency Test (1-3)	Trail-Making Test (2 & 4), Color-Word Interference Test (3)	Executive function	Trail-Making Test (4), Color-Word Interference Test (4)	Executive functions
Grooved Pegboard, fine motor functioning	Both hands	Grooved Pegboard both hands	Psychomotor speed	Grooved Pegboard both hands	Psychomotor speed
General cognitive composite score	Average across all the tests above (Z-scores)			General cognitive composite	Average across all the subtests (Z-scores)