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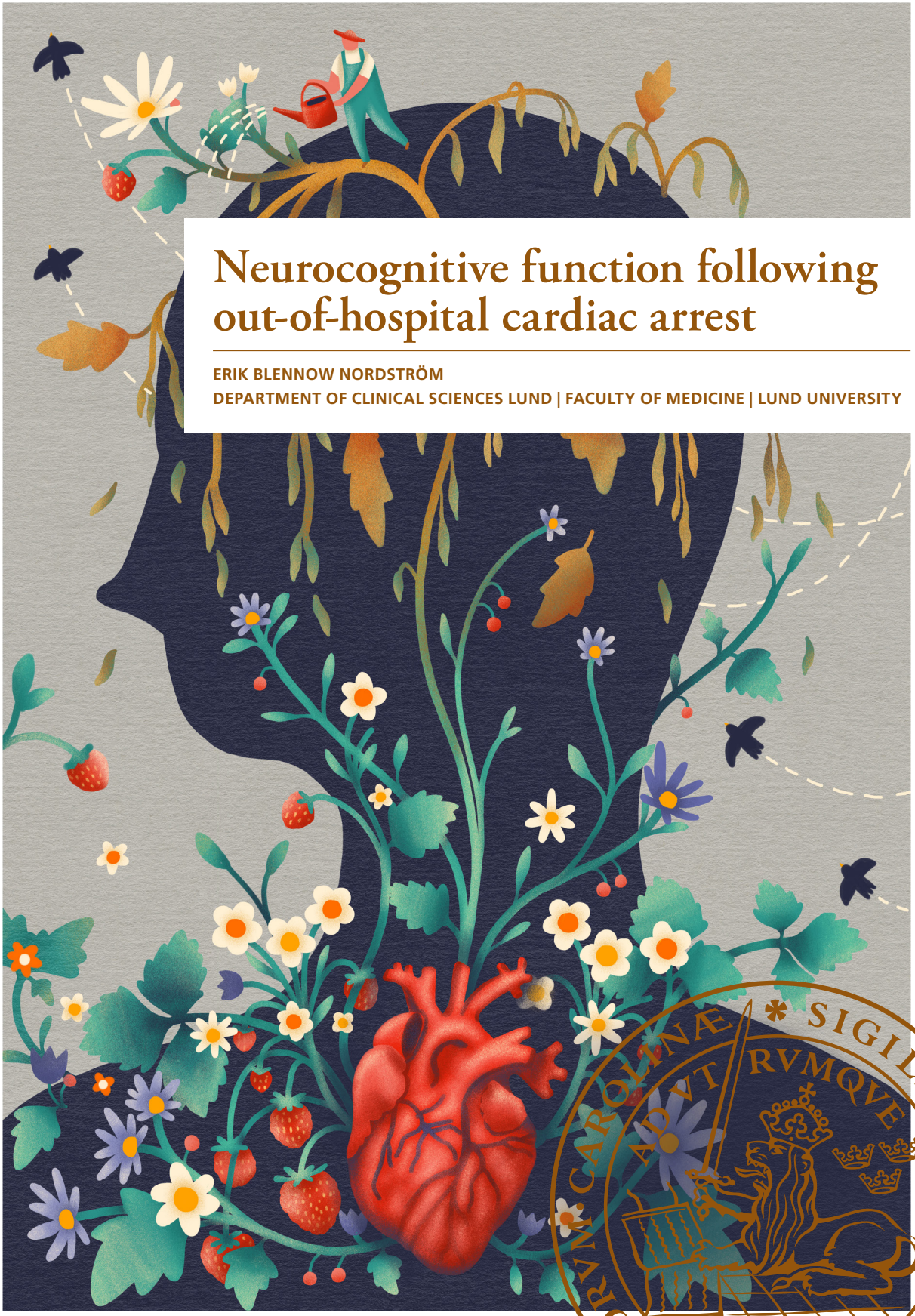

Neurocognitive function following out-of-hospital cardiac arrest

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Title Neurocognitive function following out-of-hospital cardiac arrest

Abstract

Background: The brain is susceptible to hypoxic-ischemic brain injury in conjuction with out-of-hospital cardiac arrest (OHCA). Cognitive impairments are documented in about half of all OHCA survivors, however with a pronounced heterogeneity in measurements and findings. More detailed studies and instruments that are sensitive to OHCA-related cognitive impairment, including predictive models to identify individuals at risk, are needed. It is also unclear how different neurocognitive outcome methods are related to each other, to the brain injury, and to associated factors.

Aims: The overall aim of this thesis was to explore the extent of neurocognitive impairment following OHCA in the late recovery phase. Specific aims per papers included in this thesis were: **I)** To examine the psychometric properties of an observer-reported questionnaire modified for usage after cardiac arrest, the Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest (IQCODE-CA). **II)** To explore associations between four neurocognitive outcome methods administered in the late recovery phase and early hypoxic-ischemic brain injury assessed by the biomarker serum neurofilament light (NFL), and to compare the agreement for the four outcome methods. **III)** To describe the rationale and, **IV)** report initial results of detailed assessment of neurocognitive impairment in OHCA survivors, compare the cognitive performance to a cohort of participants following acute myocardial infarction (MI), and investigate the relationship between cognitive performance and the associated factors of emotional problems, fatigue, insomnia, and cardiovascular risk factors.

Methods: I & II) Post-hoc analyses of surviving participants of the international multicenter Target temperature management 33 °C versus 36 °C after out-of-hospital cardiac arrest trial (TTM-trial), its biobank, and its cognitive sub-study, with a follow-up at 6 months post-arrest. **III & IV)** Prospective inclusion of surviving participants of the international multicenter Targeted hypothermia versus targeted normothermia after out-of-hospital cardiac arrest trial (TTM2-trial) at neuropsychological sub-study sites, recruitment of a matched non-arrest control group with acute MI, and an extensive neuropsychological assessment at approximately 7 months post-cardiac event.

Results: I) The IQCODE-CA had acceptable psychometric properties and may be used alongside with performance-based measures when screening for post-arrest cognitive impairment. **II)** The clinician-report Cerebral Performance Category was mostly related to brain injury according to NFL, but with a ceiling effect. Although associations between patient-reports and performance-based measures were weak, all four outcome methods correlated significantly with each other. **III & IV)** Cognitive impairment on neuropsychological tests was generally mild among OHCA survivors (29% had at least borderline–mild impairment in ≥ 2 cognitive domains, and 14% had major impairment in ≥ 1 cognitive domain), but most pronounced in episodic memory, executive functions, and processing speed. OHCA survivors performed worse than MI controls. Diabetes and symptoms of anxiety, depression, and fatigue were associated with worse cognitive performance among the OHCA survivors.

Conclusions: Cognitive impairment following OHCA is common. A post-OHCA follow-up service should screen for cognitive impairment using different neurocognitive outcome methods with acceptable psychometric properties. Since cognitive impairment is interrelated with emotional problems and fatigue, these areas should also be covered within routine screening. Patients with signs of impairment could be referred to neuropsychological assessment or team-based cognitive rehabilitation programs to optimize their recovery and long-term outcome.

Key words Hypoxic-ischemic encephalopathy; heart arrest; cognitive impairment; outcome

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*"The goal is **not** to obtain a test score. The goal is to **understand** how brain injury has affected higher cerebral functioning and how that information can be used to help the patient. This is the art and clinical practice of neuropsychology."*

– George P. Prigatano

Table of Contents

To our own designs of love

List of publications

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals. The papers are appended at the end of the thesis.

I. **Blennow Nordström E**, Lilja G, Årestedt K, Friberg H, Nielsen N, Vestberg S and Cronberg T. Validity of the IQCODE-CA: An informant questionnaire on cognitive decline modified for a cardiac arrest population. *Resuscitation*. 2017;118:8–14.

II. **Blennow Nordström E**, Lilja G, Ullén S, Blennow K, Friberg H, Hassager C, Kjærgaard J, Mattsson-Carlgren N, Moseby-Knappe M, Nielsen N, Vestberg S, Zetterberg H and Cronberg T. Serum neurofilament light levels are correlated to long-term neurocognitive outcome measures after cardiac arrest. *Brain Injury.* 2022;36(6):800–809.

III. **Blennow Nordström E**, Lilja G, Vestberg S, Ullén S, Friberg H, Nielsen N, Heimburg K, Evald L, Mion M, Segerström M, Grejs AM, Keeble T, Kirkegaard H, Ljung H, Rose S, Wise MP, Rylander C, Undén J and Cronberg T. Neuropsychological outcome after cardiac arrest: a prospective case control sub-study of the Targeted hypothermia versus targeted normothermia after out-of-hospital cardiac arrest trial (TTM2). *BMC Cardiovascular Disorders*. 2020;20:439.

IV. **Blennow Nordström E**, Vestberg S, Evald L, Mion M, Segerström M, Ullén S, Bro-Jeppesen J, Friberg H, Heimburg K, Grejs AM, Keeble TR, Kirkegaard H, Ljung H, Rose S, Wise MP, Rylander C, Undén J, Nielsen N, Cronberg T and Lilja G. Neuropsychological outcome after cardiac arrest: Results from a sub-study of the Targeted hypothermia versus targeted normothermia after out-of-hospital cardiac arrest (TTM2) trial. Unpublished manuscript.

Abbreviations

ABI	acquired brain injury
AUC	area under the curve
BVMT-R	Brief Visuospatial Memory Test-Revised
CI	confidence intervals
CPC	Cerebral Performance Category
CPR	cardiopulmonary resuscitation
D-KEFS	Delis-Kaplan Executive Function System
EMS	emergency medical services
HADS	Hospital Anxiety and Depression Scale
ICF	International Classification of Functioning, Disability and Health
IHCA	in-hospital cardiac arrest
IQCODE	Informant Questionnaire on Cognitive Decline in the Elderly
IQCODE-CA	Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest
MD	mean difference
MFI-20	Multidimensional Fatigue Inventory
MI	myocardial infarction
MISS	Minimal Insomnia Symptom Scale
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
mRS	modified Rankin Scale
NFL	neurofilament light
NSE	neuron-specific enolase

OHCA	out-of-hospital cardiac arrest
RAVLT	Rey Auditory Verbal Learning Test
RBMT	Rivermead Behavioural Memory Test
ROC	receiver-operating characteristic
ROSC	return of spontaneous circulation
SDMT	Symbol Digit Modalities Test
STEMI	ST-segment elevation myocardial infarction
TMT	Trail Making Test
TSQ	Two Simple Questions
TTM	targeted temperature management
TTM-trial	Target temperature management 33 °C versus 36 °C after out-of-hospital cardiac arrest trial
TTM2-trial	Targeted hypothermia versus targeted normothermia after out-of-hospital cardiac arrest trial
WAIS-IV	Wechsler Adult Intelligence Scale – Fourth Edition
WLST	withdrawal of life-sustaining therapy
WMS-III	Wechsler Memory Scale – Third Edition

Summary in Swedish – Populärvetenskaplig sammanfattning

Hjärtstopp inträffar när hjärtat plötsligt slutar slå och är ett livshotande tillstånd. Av personer som drabbas av hjärtstopp utanför sjukhus överlever endast en av tio fram till utskrivning från sjukhuset. Hjärnan har en hög ämnesomsättning och små energidepåer. Därför är hjärnan extra känslig för effekterna av ett hjärtstopp. När hjärtat slutar slå och blodet inte kan cirkulera i kroppen riskerar en hjärnskada att uppstå, till följd av syrebrist.

Många personer som överlever ett hjärtstopp kan uppleva svårigheter med att komma ihåg nya saker eller att lösa problem. Det är förenat med hjärnskadan efter hjärtstoppet. Forskning som gjorts tidigare visar att ungefär hälften av de som överlever hjärtstopp utanför sjukhus har liknande kognitiva svårigheter, det vill säga försämrad förmåga att uppfatta, komma ihåg, tänka och förstå. Svårigheterna är ofta lindriga och kan därför inte alltid omedelbart upptäckas hos de som drabbats. Kognitiva svårigheter efter hjärtstopp är associerat med nedsatt livskvalitet, minskad delaktighet i samhället inklusive minskad återgång i arbete, depression och ångest samt en ökad belastning för närstående.

Tidigare studier som undersökt kognitiva svårigheter efter hjärtstopp har använt sig av många olika mätinstrument med varierande känslighet för kognitiv nedsättning, har ofta inkluderat ett fåtal deltagare och visat på spridda resultat kring hjärtstoppsöverlevarnas kognitiva förmåga. Resultaten har därför varit svåra att tolka. Det behövs fler detaljerade studier samt fler utprövade och hjärtstoppsanpassade mätinstrument som är känsliga för kognitiv nedsättning. Dessutom finns olika metoder för att utvärdera kognition efter hjärtstopp. Det är oklart hur dessa metoder relaterar till varandra, till hjärnskadan och till andra faktorer som ofta existerar samtidigt med kognitiv nedsättning efter hjärtstopp. Till exempel är det inte undersökt genom detaljerad testning i vilken mån effekterna av hjärnskada efter hjärtstopp kan separeras från en kronisk kognitiv påverkan till följd av underliggande hjärt-kärlsjukdom. Detta beror på att hjärtstoppet kommer plötsligt och att vi inte vet hur de drabbade fungerade före hjärtstoppet.

Det övergripande målet med den här avhandlingen i ämnet klinisk medicin med inriktning neuropsykologi är att utforska förekomsten av kognitiv nedsättning efter

hjärtstopp utanför sjukhus. Avhandlingens första studie bygger på redan insamlade data från uppföljningar som genomfördes ett halvår efter hjärtstopp. De 268 individerna deltog i en kognitiv sub-studie till en stor internationell hjärtstoppsstudie, TTM-studien. Den andra studien bygger på redan insamlat material från 457 personer som deltog i TTM-studien och dess biobank. Avhandlingens tredje publikation är en analysplan för vad som skulle genomföras i den fjärde och sista studien drygt sju månader efter hjärtstopp. Här samlade vi in material i en neuropsykologisk sub-studie inom ramen för en ny stor internationell hjärtstoppsstudie, TTM2-studien. Det deltog 108 hjärtstoppsöverlevare, liksom en kontrollgrupp. Kontrollgruppen hade en liknande risk för hjärt-kärlsjukdom som hjärtstoppsöverlevarna, men hade inte drabbats av hjärtstopp och riskerade därmed inte hjärtstoppsrelaterad hjärnskada. Till kontrollgruppen rekryterades 92 personer som genomgått hjärtinfarkt.

I den första studien undersöktes ett formulär som är avsett för närstående till hjärtstoppsöverlevare. Formuläret har tidigare använts för att identifiera kognitiv nedsättning i samband med kognitiva sjukdomar (demenssjukdomar). Vi fann att formuläret med en mindre modifiering också fungerar bra för att upptäcka misstänkt kognitiv svikt efter hjärtstopp, helst i kombination med kognitiva screeningtester.

Avhandlingens andra studie använde sig av fyra olika metoder eller informationskällor om kognition efter hjärtstopp: ett kognitivt screeningtest, en klinisk skattningsskala ifylld av hälso- och sjukvårdspersonal, ett formulär för hjärtstoppsöverlevare och ett formulär för närstående. Vi utforskade hur informationskällorna relaterade till ett kvantitativt mått på hjärnskada, biomarkören NFL, och till varandra. Något överraskande visade det sig att den starkaste kopplingen fanns mellan den kliniska skattningsskalan och måttet på hjärnskadan. Det kan bero på att hälso- och sjukvårdspersonalen i sin skattning har tillgång till de andra informationskällorna samt kan ta ställning till om dessa resultat beror på nytillkommen hjärnskada eller andra faktorer som tidigare hjärt-kärlsjukdom och psykiatrisk samsjuklighet. Samtidigt är det viktigt att komma ihåg att den kliniska skattningsskalan är relativt trubbig. Den har begränsad användbarhet om syftet är att detaljerat beskriva kognition samt andra vanligt förekommande faktorer som psykisk ohälsa och trötthet. Vi visade också att de fyra informationskällorna var svagt till måttligt relaterade till varandra. Eftersom de inte helt överlappar med varandra skulle de kunna användas tillsammans för att öka känsligheten i en screening för kognitiv nedsättning efter hjärtstopp.

I de tredje och fjärde arbetena fick deltagarna genomgå en omfattande neuropsykologisk undersökning. De genomförde detaljerade kognitiva tester, fyllde i skattningsskalor om psykisk hälsa, trötthet och sömnsvårigheter samt svarade på frågor om blodtryck och diabetes. Studien bekräftar det man sett i screeningstudier – kognitiva svårigheter hos hjärtstoppsöverlevarna var vanliga, 29% var drabbade cirka sju månader efter hjärtstoppet. Grav kognitiv nedsättning förekom i 14% av fallen. De individer som hade kognitiva svårigheter hade oftast problem med episodiskt minne

(att koda in och återge saker man hört eller sett förut), exekutiva funktioner (att planera, påbörja och genomföra handlingar som kan kräva uppmärksamhet och tankemässig flexibilitet) samt processhastighet (att snabbt och korrekt bearbeta sinnesintryck, information och problem). Hjärtstoppsöverlevarna presterade sämre än hjärtinfarktskontrollerna. Förekomst av diabetes samt symtom på ångest, depression och trötthet var associerat med lägre resultat på de kognitiva testerna.

Sammanfattningsvis har denna avhandling visat att kognitiv nedsättning efter hjärtstopp utanför sjukhus är vanligt. Avhandlingen bidrar med ett praktiskt och lättanvänt formulär som närstående får fylla i för att identifiera kognitiva problem, information om hur kognitiva problem enligt fyra olika informationskällor är relaterade till varandra och till ett objektivt mått på hjärnskada tidigt i förloppet, samt med den hittills mest omfattande och detaljerade kartläggningen av vilka neuropsykologiska svårigheter som ses efter hjärtstopp.

Den kliniska innebörden av avhandlingens resultat är att patienter som överlevt hjärtstopp behöver följas även efter lyckad hjärt-lungräddning, både med kardiella och neurologiska glasögon. Störst kognitiv återhämtning sker runt de första tre månaderna efter hjärtstopp. Baserat på tidigare studier är det därför viktigt att vara medveten om att graden av kognitiv påverkan hade varit högre om vi genomfört studierna tidsmässigt närmare insjuknandet i hjärtstopp. I ljuset av detta är det nödvändigt att alla hjärtstoppsöverlevare relativt tidigt efter hjärtstoppet genomgår en screening av kognitiva svårigheter. Denna kortare screening bör bestå av flera olika informationskällor och mätinstrumenten måste vara känsliga för att indikera kognitiv nedsättning efter hjärtstopp. Eftersom kognitiv svikt är relaterat till ångest- och depressionssymtom samt trötthet behöver dessa områden också vara en fast beståndsdel i den rutinmässiga screeningen. Det är i linje med rådande svenska och europeiska riktlinjer. Först genom en screening kan osynliga kognitiva svårigheter indikeras. Det är en förutsättning för en fördjupad neuropsykologisk utredning, skräddarsydd information till patient och närstående eller teambaserad patientcentrerad kognitiv rehabilitering, där det behövs. Insatser som dessa erbjuds relativt sällan inom ramen för ordinarie hälso- och sjukvård. Vid tecken på svårigheter är de dock viktiga för att optimera den långsiktiga återhämtningen efter hjärtstopp samt underlätta för överlevaren och överlevarens närstående att återgå till ett så normalt liv som möjligt.

Preface

I started my undergraduate studies on the Psychology Program (Master of Science in Psychology Program) more than ten years ago. While finalizing this thesis, a memory of a lecture early on comes to mind. During class, our teacher asked us: "In which field of psychology do you think you will work in the future? Please raise your hands when you hear that field being called out". When the teacher called out the following potential future fields of work, I especially recall that my hand was lowered: School psychology and research. Back then, I had worked several extra hours at a special accommodation for persons with neurocognitive disorders. I became fascinated with how some persons with Alzheimer's disease lacked awareness of place and time, while they flourished when listening to music that held a deeper personal meaning to them. What made this striking personality change possible? There and then, my interest in neuropsychology began to grow, even though I had not the faintest idea that this was the name of the specialty by that time.

The years went by, and my master's thesis supervisor Susanna Vestberg invited me to present the thesis results at a frontotemporal dementia conference in Vancouver. This was another eye-opener. I had *never* guessed that a large congress hall packed with a bunch of bone-dry academics and almost as dry clinicians would feel so vibrant. This was during my practical duty as a school psychologist – yes, I had somehow changed my mind about school psychology since the aforementioned lecture. This job was thoroughly enjoyed by me, but at the conference I fully realized that data could be collected, and interventions could be recommended not only on an individual basis, but systematically on a group level as well. When introduced to the dynamic duo of Tobias Cronberg and Gisela Lilja, all things seemed to fall into place. Or rather, this was the beginning of the work behind this thesis. After a brief but lovely temporary employment at a Memory clinic, I started working at the university hospital adult in-patient brain injury rehabilitation unit. The causes of the moderate to severe brain injuries were varying; some patients had suffered a hypoxic-ischemic brain injury following cardiac arrest. The patients at the unit were obviously not representative of the entire population of persons surviving a cardiac arrest, but I was baffled by the heterogeneity of the cognitive, emotional, and behavioral sequelae after a successful resuscitation. What Gisela and Tobias had explained to me earlier was now evident to me as a clinician as well. We still needed to know more about the neurocognitive function of the individuals surviving cardiac arrest and follow them over a longer

timeframe with a great span of sensitive tests. This was the foundation of Papers III and IV in this thesis, a neuropsychological sub-study of the largest randomized trial to date on the use of temperature control in post-cardiac arrest care. After lengthy preparations and the formation of a highly competent team of collaborators much thanks to my supervisors, the first neuropsychological sub-study participant was included on a hot summer's day 2018. Since then, I have personally met another 35 participants surviving cardiac arrest and almost as many participants in the control group. Not only did the participants contribute by undergoing the neuropsychological assessment but also by informally sharing their experiences of the aftercare. We were thrilled when other hospitals started to include participants too. Coordinating a clinical trial like this was not without its caveats, but the combined know-how of the enlarged team and the commitment of the participants made it possible.

The two other papers in this thesis came into fruition as a way of bringing partly other perspectives on neurocognition following cardiac arrest into the picture. The network of the individual is significant for the rehabilitation and could contribute with an important perspective on the current cognitive function of the individual surviving cardiac arrest. This notion is what led us to design Paper I. Paper II on the other hand aimed to investigate the relationship between different perspectives on neurocognitive outcome in individuals surviving cardiac arrest. The results on the outcome perspectives were compared with levels of a sensitive biochemical marker of brain injury. This explorative study was surprisingly exciting to get engulfed by, and a godsend when clinical research was put on hold during the COVID-19 pandemic. The study also offered an excellent opportunity to include a neurobiological method in the thesis.

This thesis in clinical medicine with a focus on neuropsychology has been carried out in parallel with my clinical work as a psychologist, most recently at the university hospital out-patient neurorehabilitation unit. From a broader perspective, clinical research can change scientific guidelines that in turn can change clinical practice. Still, when meeting individual clinical research participants, clinical research could uncover problem areas that might not have been identified by regular healthcare so that further support or rehabilitation could be offered. This has been a cornerstone of our research group, and on our sites in southern Sweden alone we have sent around 20 referrals for cognitive problems, emotional problems or fatigue to primary care and rehab units within the neuropsychological sub-study.

In my PhD studies, I have now come full circle by having the fantastic opportunity to teach at the Psychology Program. Hopefully I have contributed with enthusiasm on how clinical psychological research could contribute to the individual outcome of a patient in the long-term, if only faintly. So, the next time the psychology students are asked by a teacher to raise their hands when hearing a potential future field of work, who knows? Maybe even a few more students might wave their hands when research is called out. I am glad I changed my mind.

Background

Etiology and epidemiology of cardiac arrest

Types of cardiac arrest

According to the Utstein definition, cardiac arrest is the cessation of cardiac mechanical activity, confirmed by the absence of signs of circulation [1, 2]. If resuscitation attempts are unsuccessful, this is referred to as sudden cardiac death. Successful cardiopulmonary resuscitation (CPR) may lead to sustained return of spontaneous circulation (ROSC). Cardiac arrests are often categorized into two groups depending on the location of the arrest; in-hospital cardiac arrest (IHCA) occurs during hospital admission, while out-of-hospital cardiac arrest (OHCA) occurs on all other places that is not a hospital. Patients who experience an IHCA tend to have a witnessed arrest and be attended by professional first responders to a higher degree than those who experience an OHCA [3]. Although a recent Danish study found an overall similarity in patient demographics and most comorbidities when comparing patient characteristics between OHCA and ICHA [4], IHCA has traditionally been considered as a distinct disease entity, partially since these patients are already receiving in-patient hospital care. Acute coronary syndrome and other cardiac causes represent the largest proportion of causes of OHCA in adults > 40 years, whilst respiratory failure is the most common cause of IHCA [5]. The investigations within this thesis have included OHCA participants only.

Causes of cardiac arrest

Cardiac arrests can also be classified according to etiology. Most patients reached by emergency medical services (EMS) have a cardiac cause, for example, myocardial ischemia [6]. Cardiac arrest of presumed cardiac causes mostly appear to be triggered by thrombi or coronary plaque disruption, which leads to acute occlusion [7]. In Sweden, the main causes of OHCA are cardiac among adults ≥ 65 years, while the causes in ages 16–40 are more diverse including intoxications, trauma, and cardiac causes [8].

Cardiac causes of cardiac arrest are commonly sub-categorized by their initial recorded rhythm on an electrocardiogram. In ventricular fibrillation, the ventricles, the lower

chambers of the heart, quiver or twitch which prevents them from pumping. In ventricular tachycardia, the ventricles contraction is so rapid that the heart cannot refill. These two cardiac rhythms are considered shockable; arrests may be reversed if CPR is performed, or if a defibrillator shocks the heart and restores the heart rhythm so that the blood again can circulate around the body. Two rhythms are grouped together as unshockable rhythms: In pulseless electrical activity, there is no detectable pulse despite electrical activity on the electrocardiogram, while asystole is defined as a nearly flat line. Patients with unshockable rhythms have a worse prognosis than those with ventricular fibrillation as their first rhythm [5], and shockable rhythms are associated with performed bystander CPR after witnessed arrests [9]. Over time, there has been a shift of initial recorded rhythms from a majority of shockable rhythms to those that are not shockable [10]. According to the Swedish Heart-Lung Registry, this could be explained by longer duration until EMS arrival, since shockable rhythms are converted to unshockable in due course [8].

Epidemiology and survival

The OHCA incidence where CPR is attempted is usually estimated to 50 per 100,000 in the general population but varies throughout the world [5, 11]. Each year, there are around 275,000 cases of OHCA in Europe and 355,000 cases in the United States [5, 12]. The average adult survival rate is poor with an estimated global 1-year survival rate of 7.7%, 95% CI [5.8–9.5%] [13], again with large local and national variations even within the same continent [11].

Despite more initial rhythms associated with worse prognosis, survival figures are stable or have improved the last decades; more patients are admitted alive to the hospital and the 30-day survival or survival to hospital discharge is generally greater [5, 11]. In 2000, 4.44% of Swedish patients survived 30 days following OHCA, while this was the case for 10.46% of patients in 2020 [8]. Possible causes for this are early recognition, improved bystander CPR due to training in the communities and dispatcher-assisted CPR, improved intensive care, and availability to automated external defibrillators in public locations [14, 15].

Survival of cardiac arrest depends on a sequence of time-sensitive interventions. To promote these interventions and to maximize the chance of survival, the rescue chain (die Rettungskette) was described by the German professor Ahnefeld in 1970 [16, 17]. It was built upon as the Chain of survival in the 1980s and 1990s, and has since become a well-known concept [18]. The critical steps to optimize outcome following OHCA constitute the links of the chain.

Fig. 1 The European Resuscitation Council adult out-of-hospital cardiac arrest chain of survival [19]. Reproduced with permission. Copyright (2006) Elsevier.

The original links included activation of the emergency response, provision of early high-quality CPR, early defibrillation, and advanced life support interventions. The chain was revised in 2005 with an increased focus on recognizing and preventing cardiac arrest, and on effective post-resuscitation care including careful prognostication (Fig. 1) [19]. The greatest potential to improve survival can mainly be attributed to the two first links of the chain [20]. Nevertheless, in the latest American Heart Association version of the chain from 2020, it recognized support during recovery and survivorship as a contributor to the ultimate functional survival [21].

Pathophysiology

Post-cardiac arrest syndrome

When the blood flow stops during cardiac arrest, a myocardial dysfunction occurs – but the entire body is exposed to ceased cardiac output and oxygen delivery due to a period of no-flow, the elapsed interval between collapse and onset of CPR, and low-flow, the elapsed interval between onset of CPR and restoration of circulation. The ischemic injury accumulates over time since CPR does not generate enough output to sustain normal blood flow, so again, time matters for a successful resuscitation as demonstrated in Fig. 2. The duration and cause of cardiac arrest contribute to the outcome, with post-cardiac arrest syndrome as a possible consequence. The post-cardiac arrest syndrome was first described by Negovsky in the 1970s [22]. As defined by the International Liaison Committee on Resuscitation, the syndrome comprises the following overlapping pathophysiological processes: 1) brain injury, 2) myocardial

dysfunction, 3) systemic ischemia/reperfusion response, and 4) persistent precipitating pathology [23]. The myocardial dysfunction usually starts to recover by 2–3 days, although full recovery may take significantly longer [24]. The systemic ischemia/reperfusion may contribute to multiple organ failure and infection, thus having many sepsis-like features [25].

Brain injury is a main component of the post-cardiac arrest syndrome. The brain injury can be divided into a primary ischemic injury and additional secondary reperfusion injury if blood flow is partially reinstituted during resuscitation.

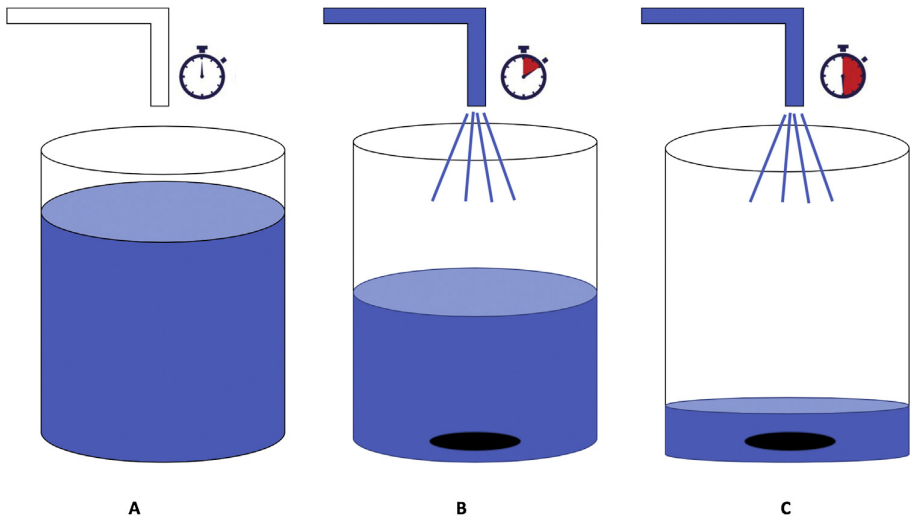

Fig. 2 Time matters for a successful resuscutation. A bucket of water, that may symbolize oxygen and glucose supplies, and a faucet, that may symbolize resuscitation attempts and meager refills of supplies, illustrates the time-dependent likelihood of clinical outcomes after cardiac arrest. **A:** A full bucket at the onset of cardiac arrest. **B:** After elapsed no-flow, in which water drains out of the bottom of the bucket, resuscitation begins and new water fills the bucket. **C:** After elapsed low-flow, the rate of drainage has outpaced the rate of filling and the bucket approaches empty [26]. Reproduced with permission. Copyright (2020) Elsevier.

Primary ischemic injury

Many tissues in the body can survive prolonged periods of time without oxygen, but the brain needs a continuous supply of oxygen and glucose to function. The brain represents 2% of the body weight but accounts for 15–20% of the total body metabolism [27, 28]. Thus, the neurons have a high metabolic demand, but since they have no in-built glucose stores, consciousness is lost within seconds of absent cerebral blood flow [29]. The post-cardiac arrest brain injury is of hypoxic-ischemic nature; the insufficient blood flow (ischemia) and insufficient oxygen delivery (hypoxia) during cardiac arrest may result in neuronal cell death. After initial selective synaptic failure due to impaired presynaptic neurotransmitter release, stores of high-energy substrate

adenosine triphosphate are depleted, which in turn results in dysfunctional transmembrane Na^+/K^+ ion pumps which are adenosine triphosphate dependent [30, 31]. Influx of Na^+ leads to cell swelling and intracellular oedema, is followed by K^+ efflux and membrane depolarization which causes inability to produce action potentials, with subsequent influx of Ca^{++} into the intracellular space, mitochondrial dysfunction, and overproduction of free radicals [27]. Pathologic acid accumulation (acidosis) and excess glutamate release leads to overexcited receptors (excitotoxicity).

Secondary reperfusion injury

As described by the post-cardiac arrest syndrome, successful restoration of circulation may trigger reperfusion injury. Here, free radical formation and nitric oxide toxicity ensues, with a risk of continued brain cell injury and neuronal cell death.

It is largely unknown to which extent the pathophysiological processes that lead to permanent brain damage may be reversed. Initial synaptic failure and cell swelling may be reversed with quick reperfusion, with timely interventions also needed to hinder delayed neuronal death (apoptosis) [30].

Areas vulnerable to brain injury

Certain neuroanatomical regions are more vulnerable to hypoxic-ischemic brain injury than others. This is possibly due to higher metabolic activity and neuronal demand of oxygen and nutrients in these regions, such as the hippocampi in the medial temporal lobes, pyramidal neurons in cortical layers III, V, and VI, the thalami, striatum of the basal ganglia, and Purkinje cells of the cerebellum [32, 33]. Susceptibility to damage could also be related to greater distance from the main arterial supply, resulting in less tolerance of relative ischemia in border zones between the two arteries (watershed regions of the cortex) [34].

The concept that certain brain regions are more vulnerable to injury is referred to as the selective vulnerability hypothesis. Its validity following cardiac arrest in humans is still debated due to much evidence emerging from animal models and diverse anoxic conditions [35, 36]. It has been hypothesized that brain injury following cardiac arrest is abrupt and complete, and therefore leads to more widespread damage than other hypoxic injuries such as carbon monoxide poisoning [36, 37]. Still, brain regions respond differently to the oxygen deprivation over the course of time. Whilst necrosis in the basal ganglia and cortex emerges shortly following cardiac arrest, ischemic change in the hippocampi appear to be delayed within a few days of reperfusion, and areas such as the brain stem seemingly recover faster or are more resistant of post-cardiac arrest brain injury [33, 35, 38, 39].

Post-cardiac arrest care

Targeted temperature management

Targeted temperature management (TTM) can be defined as any strategy that aims to achieve and maintain a specified body temperature, typically from 33 to 37.5 °C [27]. TTM at hypothermic levels was implemented as a neuroprotective post-cardiac care intervention in resuscitation guidelines following two clinical trials published in 2002. These landmark trials found that patients treated with TTM at 33 °C for 12–24 hours after OHCA had an improved neurologic outcome compared to patients without active temperature control [40, 41]. One of the trials also reported a reduction in mortality [40]. Still, the trials were relatively small (n = 275; n = 77) and only included patients with shockable initial recorded rhythms (ventricular fibrillation or pulseless ventricular tachycardia).

In 2013, results from the large international Target temperature management 33 °C versus 36 °C after out-of-hospital cardiac arrest trial (TTM-trial) showed no difference in mortality or neurologic outcome between cooling to 33 °C and 36 °C following OHCA of presumed cardiac cause [42]. Here, 80% of included patients had shockable initial recorded rhythms. A large 2019 trial consisting of randomized cardiac arrest patients with non-shockable initial recorded rhythms however reported similar mortality but higher rates of good neurological outcome in the 33 °C group compared to the 37 °C group [43]. The to date largest study on the use of TTM in post-cardiac arrest care was published in 2021. The Targeted hypothermia versus targeted normothermia after out-of-hospital cardiac arrest trial (TTM2-trial) reported no benefit of targeted hypothermia at 33 °C on all-cause mortality or functional outcome, when compared to targeted normothermia [44].

Several recent systematic reviews and meta-analyses have highlighted that the use of TTM is not supported by current research [45-50], instead reporting an increased risk of arrythmias [46-48]. Taking this into consideration, the International Liaison Committee on Resuscitation updated their treatment recommendations [51]. European guidelines were rapidly updated based on this report in 2022. Currently, the evidence is considered insufficient to recommend for or against temperature control at 32–36 °C or early cooling after cardiac arrest in patients who remain comatose after cardiac arrest, but continuous monitoring of core temperature and active prevention of fever (defined as a temperature > 37.7 °C) for at least 72 hours is recommended [52]. Although the investigations included in this thesis do not evaluate TTM, they consist of participants from both the TTM-trial and the TTM2-trial. Therefore, these trials are further described in the Methods section.

Neurological prognostication

Comatose cardiac arrest patients are generally transferred to intensive care units to stabilize their vital functions. Since structures in the central nervous system may be damaged following cardiac arrest, a multimodal neuroprognostication that predicts post-arrest outcome is considered the most reasonable approach to assess the utility of further intensive care [53]. The neuroprognostication often includes clinical neurological examinations, electroencephalography, somatosensory evoked potential, neuroimaging, and biochemical markers of brain injury [54]. Neuroprognostication is central for making decisions of withdrawal of life-sustaining therapy (WLST) [55], so that care of patients with severe and irreversible brain injury without a chance of a neurologically meaningful survival can be avoided [27]. In large parts of the world, WLST due to presumed extensive brain injury accounts for the majority of deaths following OHCA resuscitation [56].

Biomarkers of brain injury

The context of post-arrest injury biomarkers

Biochemical markers of brain injury may be used to predict poor and good neurologic outcome in a multimodal setting [57-59]. These biomarkers are sampled in blood (serum or plasma) or cerebrospinal fluid. Blood is more accessible than cerebrospinal fluid [60].

Clinically available post-arrest biomarkers

The latest European algorithm for post-resuscitation care recommends serial measurements of neuron-specific enolase (NSE) in serum, where increasing values between 24 h and 48 h and 72 h in combination with high levels at 48 h and 72 h indicate a poor prognosis [54]. NSE is present in the neuronal cell bodies but may be found falsely elevated in hemolytic samples (hemolysis; the breakdown of red blood cells with subsequent release of hemoglobin) since NSE is also located in the red blood cells [61]. Elevated serum NSE has been associated with generalized brain oedema on computer tomography and pathologic electroencephalography patterns [62, 63].

Biomarkers of interest when investigating brain injury after cardiac arrest are not exclusively located to the neuronal cell body. For instance, elevated S100B is a possible and commonly examined predictor of poor post-arrest outcome [64]. This calcium-binding protein is released from glial cells such as astrocytes and Schwann cells but also from outside of the nervous system.

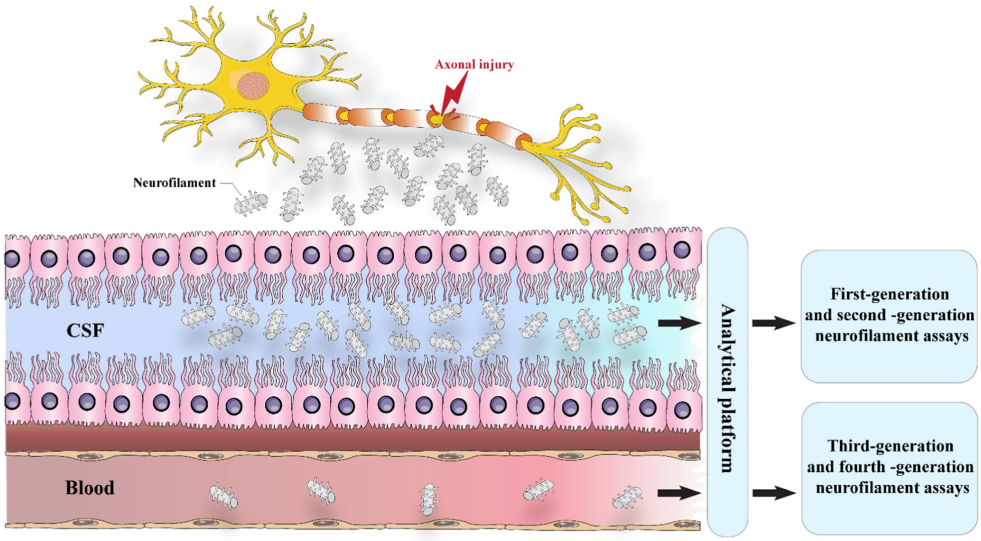

Fig. 3 The release of neurofilament from the neuron after axonal injury. Cytoskeletal proteins, such as neurofilaments, are released into the cerebrospinal fluid (CSF) and, at lower levels, in the peripheral blood upon neuroaxonal damage. First-generation and second-generation immunoassays are able to measure neurofilaments in the cerebrospinal fluid but have low sensitivity for detection in the blood. So called third-generation (electrochemiluminescence) and fourth-generation (single-molecule array) methods can detect blood concentrations of neurofilaments and measure subtle longitudinal alterations in healthy controls and in pathological cases [65]. Reproduced with permission. Copyright (2020) Springer Nature.

Neurofilament light

Neurofilament proteins maintain neuronal structure in the neuronal cytoplasm and are mainly present in large myelinated axons but also in dendrites and the neuronal cell bodies. Neurofilaments are classified into subunits based on their molecular weight. Neurofilament light (NFL) is often elevated in conditions such as frontotemporal neurocognitive disorder, Alzheimer's disease, multiple sclerosis, traumatic brain injury, and polyneuropathies, indicating that NFL is a sensitive but unspecific marker of axonal injury [66-70]. See Fig. 3. NFL is also present at low concentrations in healthy controls and is increasing as a function of age, with marked individual differences [68, 71]. Age-stratified normal reference intervals for NFL in plasma based on data from several cohorts were recently established [72]. This will increase the clinical utility of plasma NFL.

Although standardized analyses do not yet exist, NFL has gained increasing interest within post-arrest neuroprognostication over the past number of years. Small pilot studies have found increased neurofilament levels in cerebrospinal fluid and blood, even when samples were analyzed with standard assays [73-75]. Three recent larger studies that used sensitive assays have reported promising prognostic abilities of NFL following cardiac arrest, superior to other biomarkers: Serum NFL levels above 641.4 pg/ml at 24 h post-OHCA have shown a 99% specificity for poor outcome in a post-hoc analysis

of a multicenter trial [58]. A post-hoc analysis of another multicenter trial reported higher NFL levels at 48 h in patients with poor 6-month outcome compared to those with good outcome [76]. A prospective single-center study reported similar results with NFL sampled at 24 h post-OHCA and neurological outcome at hospital discharge [77]. Furthermore, a smaller retrospective single-center study has indicated that serum NFL can differentiate severe hypoxic-ischemic brain injury according to the European prognostication algorithm from other causes of poor outcome with 91.7% specificity [78]. NFL levels are also associated with electroencephalography patterns after cardiac arrest [79]. In sum, NFL is the currently most accurate biomarker to indicate hypoxic-ischemic brain injury following OHCA. However, the relationship between the post-arrest brain injury and standardized neurocognitive outcome methods has not been extensively researched. In this thesis, we used NFL to explore the associations between the early brain injury and neurocognitive outcome methods administered in the later phase of recovery.

Outcome following cardiac arrest

Prehospital, hospital, and demographic factors

Cardiac cause of death following cardiac arrest may be more common during the first days after admission to hospital, while the extent of the hypoxic-ischemic brain injury is decisive for the long-term prognosis once circulation has stabilized. WLST due to severe hypoxic-ischemic brain injury is a major cause of death of hospitalized cardiac arrest patients [80]. Besides non-shockable initial rhythm and poor outcome according to multimodal neuroprognostication, there are other predictors or determinants of mortality, including older age, cardiac arrest occurring at home, no bystander CPR, and longer time from EMS dispatch until EMS arrival [81, 82]. Frailty, that is, a clinical geriatric syndrome with risk of accelerated biological aging and increased vulnerability to physical, psychological, and social stress, has been associated with poorer long-term outcome such as worse survival and increased depression symptoms among IHCA survivors and after critical illness [83, 84]. Current evidence on the impact of frailty on OHCA outcome appears lacking. Delirium, which is common during intensive care, is related to long-term cognitive impairment and may be a causative factor that leads to cognitive decline [85, 86], but this again warrants further investigation among OHCA survivors. Post-arrest myocardial dysfunction, even in the absence of earlier cardiac disease, may also lead to a worse prognosis but could just reflect the degree of ischemic injury following severe cardiac arrest [87]. Cardiac arrest-induced posttraumatic stress symptomatology has been associated with higher risk of death and cardiovascular events in a single study, but these findings need to be reproduced [88]. Variables such as worse

cognitive reserve (characterized by premorbid intelligence quotient, educational, and/or occupational attainment) and lack of family support have been associated with poorer outcome following other non-progressive acquired brain injury (ABI) [89, 90]. Yet, this has not been investigated specifically for cardiac arrest survivors.

Other demographic factors influence post-OHCA outcome. Inhabitants of neighborhoods with lower socioeconomic status are less likely to receive bystander CPR [91]. Furthermore, worse education and unemployment has been associated to lower rates of survival with good neurologic outcome, but this may be attributable to hospitals in communities with lower socioeconomic status providing inadequate post-arrest care [92].

There is no consensus in OHCA outcome related to sex differences, as some studies report better survival for men and others report better survival for women. Recently, a cohort study and a meta-analysis both found that women less often receive bystander CPR, and when they do, they have lower survival rates, likely because of a lower rate of shockable initial rhythms compared with men [93, 94]. This, in combination with the fact that shockable rhythms deteriorate to asystole if left untreated, indicates that OHCA recognition in women is insufficient.

Functional status and quality of life

In countries where WLST is common, the long-term neurological and functional outcome following OHCA is generally good [42, 44, 95, 96]. This includes outcome in terms of quality of life as well [97]. There is limited information on longitudinal change, with a recent study suggesting that functional outcome can be improved up to 18 months post-arrest [98]. Impairments have, however, been reported in 20% of survivors when it comes to more complex activities (instrumental activities of daily living) around three years after OHCA [99]. The findings are mixed. OHCA survivors report more restricted societal participation and lower return to work than ST-segment elevation myocardial infarction (STEMI) controls at 6 months, with limitations in participation in about half of OHCA survivors [100]. OHCA survivors who have received bystander-CPR report better health-related quality of life than those who have not [101]. Long-term survival is positively correlated with less deterioration in functional status and activities in daily living [102]. There are little data on the long-term survival after OHCA; a recent systematic review and meta-analysis reported estimated survival rates at 10 years between 62% and 64% in patients surviving the initial hospital stay after OHCA of a presumed cardiac cause [103]. In countries that infrequently practice WLST, a poor outcome as a consequence of the hypoxic-ischemic brain injury is common [104].

Caregiver burden

Although OHCA survivors rarely remember their collapse, family members often witness the event and may be involved in contacting EMS or performing bystander CPR [105]. Caregivers are suggested to have higher levels of post-traumatic stress symptoms than OHCA survivors and may have psychological difficulties, feeling obligated to monitor and prevent a new cardiac arrest [99, 106, 107]. There exists some evidence that survivors and families perceive that post-arrest care services do not provide accurate information about sequalae and only offer limited follow-up with inconsistent access to health care [108]. Whilst overall caregiver quality of life at 2 years post-arrest has been reported as being similar to that of the general population, caregivers who witnessed the collapse or performed CPR have greater levels of post-traumatic stress than those who did not witness the collapse [109]. The cognitive function and functional dependency of the cardiac arrest survivor impact the caregiver's burden and quality of life [110].

Measuring outcome

When reporting outcome after cardiac arrest, crude clinician-reported summaries of functional outcome have typically been used. International recommendations on a core outcome set in cardiac arrest survivors were developed in 2018 by the International Liaison Committee on Resuscitation [111]. Yet, these recommendations are limited to recommending reports of survival to hospital discharge or 30 days, the clinician-reported modified Rankin Scale (mRS) assessing functional outcome [112], and one of three shortlisted health-related quality of life patient-reports. The Montreal Cognitive Assessment (MoCA) [113], a cognitive performance-based screening measure, has in European guidelines been suggested as a cognitive screening within the first three-months after hospital discharge [54].

Cognition

Measuring cognition – a framework

According to a influential 1967 definition, cognition "refers to all processes by which the sensory input is transformed, reduced, elaborated, stored, recovered, and used […] including such terms as sensation, perception, imagery, retention, recall, problem solving, and thinking" [114]. In reductionist terms, cognition can be defined as a collection of mental processes such as perception, attention, and memory. The study of the brain–cognition relationship has increasingly become mutually important during

the last decades, as techniques for studying how the nervous system affects behavior have become available.

Cognitive outcome methods

The United States Food and Drug Administration describes four methods or perspectives to assess outcome, categorized by the source of information [115]. These methods could be used to report outcome in general, but are here described focused on cognitive outcome.

- Performance-based measures – outcome according to test results
- Clinician-reports – outcome reported by health-care professionals
- Patient-reports – outcome reported by patients or participants themselves
- Observer-reports – outcome reported by informants/proxies, such as relatives or friends, that observes the patients or participants regularly in daily life

Performance-based measures

Performance-based measures are sometimes referred to as objective, though this may be a misleading term – the "objectivity" is dependent of acceptable psychometric properties such as validity and reliability. Rather, performance-based or direct measures are more suitable descriptions. There are several ways to assess cognition by performance-based measures.

Neuropsychological tests are traditionally considered as the criterion or gold standard when measuring cognition [116]. These detailed measures have been associated with brain functions or processes [117], see Fig. 4 for an overview. They should also be administered under highly standardized conditions, often measuring accuracy and/or response times. Many neuropsychological tests include a range of items reflecting the lower and upper end of the scale (i.e., avoiding floor and ceiling effects), so that reliable population norms based on the normal distribution can be extracted and to identify patterns of strengths and difficulties.

Screening measures are broadly used to detect an attribute. Acceptable diagnostic accuracy is required for a screening measure [118]. Screenings should emphasize sensitivity in favor of specificity, while also taking time-efficiency (feasibility) into consideration [119]. Cognitive screening measures are often used to identify patients with potential problems, further evaluated by more detailed neuropsychological tests.

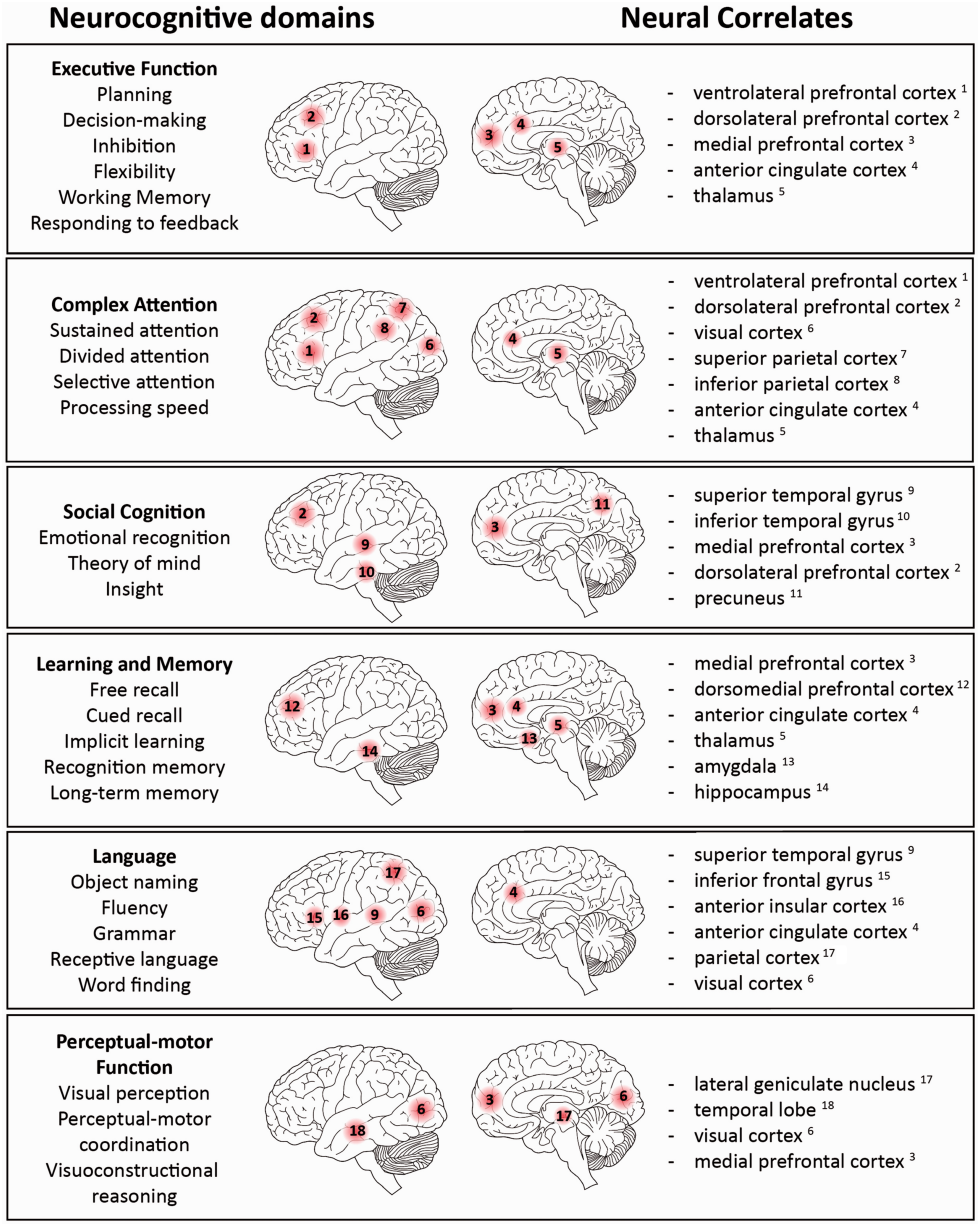

Fig. 4 A sketch of neurocognitive domains and their neural correlates. Multiple areas and networks may be injured by a lesion since the brain regions are widely distributed, frequently intersecting and overlapping [120]. Reproduced with permission. Copyright (2019) World Stroke Association.

Functional cognitive assessments are activity or participation based cognitive assessments that also could be considered as detailed performance-based measures. This approach uses behavioral observations in a naturalistic but controlled setting to examine how cognitive processes are used in a realistic daily life activity task [121]. These assessments have a high ecological validity since they assess how the person integrates cognitive functions to perform a complex activity. They are often not standardized but exceptions exist [122].

Clinician-reports

Clinician-reports are often used in clinical trials following cardiac arrest, where the clinician is instructed to report a summary of their perception of the participant's overall functional outcome on an ordinal hierarchical outcome scale, that typically contains 5–8 categories of outcome. As clinicians mostly have limited ability to observe functional outcome, they collect information on symptoms, everyday life activities, and participation by shorter clinical observations and interviews with patients, relatives, or other health care professionals. Information from medical records could also be used. Clinician-reports may utilize other direct or indirect ways to assess outcome such as cognition, emotion, and health-related quality of life, based on behavioral data. Although scored by a health-care professional, the most common clinician-reports have been criticized as rudimentary or crude, so that important cognitive impairment is not identified [123, 124].

Patient-reports

Patient-reports seek to understand how patients feel, function, and live their lives in relation to health challenges and associated healthcare [125]. Patient-reports may be generic (e.g., reporting several conceptual domains) or specific in their outcome reporting (e.g., reporting specifically cognitive outcome).

Observer-reports

Observer-reports are standardized measures that are completed by a proxy who has prior knowledge of the patient. Observer-reports are often based on observation of everyday activities of the patient.

Cognition following OHCA

Prevalence of cognitive impairment

There was a limited focus on cognitive and neuropsychological impairments following cardiac arrest until the 1990s, but this changed with improved survival ratios [126]. A seminal systematic review of 28 studies from 1980 to 2006 established that there was a large heterogeneity concerning post-arrest cognitive outcome, with study sample sizes

usually below 50 subjects and a high risk of bias within study samples [127]. The prevalence of cognitive impairment ranged from 6 to 100%. In three high quality prospective cohort studies, the cognitive impairment range was 42–60% [128-130]. Therefore, subsequent studies often report that cognitive sequelae are documented in about half of all survivors. An updated systematic review of the literature from 2006 to 2021 identified 43 studies that included cognitive assessment following OHCA [131]. Although the risk of bias within the studies was lower in the latter systematic review, results were overall comparable. The proportion of participants with cognitive impairment again differed greatly between studies, from 0 to 88%, with the studies in the lower and upper extreme both having very small sample sizes (n = 9 and 8, respectively) and a high risk of bias [132, 133]. Several studies that report cognitive outcome following OHCA either include a larger number of participants and utilize screening measures [134], or include a small sample with more sensitive measures [135]. Most studies do not include a control group, which could make it possible to separate cardiovascular risk factors shared in both groups from arrest-specific hypoxic-ischemic brain injury if using a cardiac non-arrest control group. Cardiovascular risk factors and post-intensive care syndrome are both associated with cognitive impairment [136, 137]. Furthermore, there is a diversity of measures used (> 50) and cognitive domains assessed in post-arrest studies, a lack of estimation of the premorbid function of the participants, the follow-up assessment points differ from study to study, and there is a diversity of impairment criteria used across studies [131]. Short time to awakening was the only consistent factor associated with a better long-term cognitive outcome in the first systematic review [127]. Later works have instead reported conflicting results. Some findings associated shorter coma duration with better performance-based cognitive outcome [123, 138], and others reported non-significant results in that regard [139, 140].

Cognitive function per cognitive domains

Among the cognitive domains, post-OHCA impairments in memory functions are most often observed, followed by executive functions and processing speed [131]. As for memory specifically, deficits in immediate and delayed recall (sub-components of episodic memory) generally appear more frequent than impaired short-term working memory or recognition [131]. Some studies have, however, found no significant differences between these memory functions [138, 141]. Tests of processing speed are overall sensitive to, but not impairment-specific to, ABI [117]. Executive functions following OHCA are often assessed with measures of planning, cognitive flexibility and inhibition, but also verbal fluency if this function is allocated to the executive domain and not the verbal domain [131]. Memory, executive functions, and processing speed are, nevertheless, the most thoroughly investigated cognitive domains after OHCA. Some claims that earlier studies overemphasize deficits in memory functions [142]. Smaller studies indicate that verbal functions such as reading, writing, verbal

abstraction (and verbal fluency) as well as visual/constructive functions may be additionally impaired [128, 143-145]. It has been hypothesized that survivors of OHCA with cognitive impairment either have deficits in memory, processing speed, and executive functions only, or that they have significant impairments in all cognitive domains that could impact on daily function and lead to debilitating disability [146]. This bimodal pattern of cognitive impairment is known following non-OHCA hypoxic-ischemic brain injury as well [147], but the data on different cognitive profile clusters are however almost absent. Overall, the post-OHCA cognitive profile should be investigated with sensitive tests, measuring a wider array of cognitive domains, and including a larger number of participants than most earlier studies in this field.

Long-term cognitive function

As is the case with other ABI, the highest proportion of cognitive impairment is generally found in the early sub-acute period following OHCA. Cognitive impairment ratios of 80–100% have been reported before or shortly after hospital discharge [148, 149]. However, some studies with assessment points during the first days and weeks after OHCA have described a lower prevalence, 54–60% [150-152]. The majority of works have assessed cognitive outcome once per cohort. Among those who have had a longitudinal design, most cognitive recovery occurred in the first three months post-OHCA, with relatively stable results during re-assessment at one year [128, 135, 150]. The number of studies that use neuropsychological tests to investigate changes > 12 months is scarce. Again, there is a diversity of assessed cognitive domains and impairment criteria between studies.

Post-OHCA cognition in relation to associated factors

The association between cognition, emotional problems, fatigue, cardiovascular risk factors, and OHCA is complex. There is an increased risk of mood disorders following OHCA. A recent meta-analysis found pooled overall prevalence rates of anxiety at 26%, 95% CI [16–39%], depression at 19%, 95% CI [11–30%], and post-traumatic stress symptomatology at 20%, 95% CI [3–30%], greater than the approximate prevalence in the general population [153]. According to the meta-analysis, the prevalence of anxiety and depression symptoms following OHCA increased over time, suggesting that timed interventions are important. Although rates varied considerably between studies, they were within the overall span of an earlier systematic review [154]. One study has found similar rates of anxiety and depression among survivors of OHCA and STEMI [155]. Depressive symptoms are considered to be more associated with perceptions of negative recovery than cognitive and functional measures among the survivors of OHCA themselves [156]. On that note, patient-reported cognitive impairment has been more related to emotional problems than performance-based tests

of cognition following ABI [157]. This has not been investigated specifically post-OHCA.

Emotional problems are associated with the onset of cardiovascular disease and diabetes [158, 159]. Anxiety symptoms could thereafter partly predispose to cardiac arrest, possibly due to risk factors such as unhealthy lifestyle and metabolic abnormalities [160]. Cardiovascular disease and diabetes are related to a higher risk of cognitive decline in general [136, 161]. Hypertension in particular has been associated with major neurocognitive disorder due to vascular disease and Alzheimer's disease [162]. Meanwhile, essential lifestyle changes, such as physical activity, smoking cessation, and risk factor treatment, following onset of cardiovascular disease are dependent of the cognitive and emotional status of the patient [163]. Cardiac anxiety after cardiac arrest, such as hypervigilance of changes in heart rate or blood pressure, may be followed by behavioral avoidance, which in turn further increases the risk of secondary cardiovascular diseases [164]. The brain and heart also share common risk factors, for example hypertension, diabetes, smoking, physical inactivity, and dyslipidemia, and are similarly affected by systemic inflammation, ischemia due to atherosclerosis, and dysfunction of the neuroendocrine system [165]. Pathophysiological activations of stressors are more pronounced in women than men. Yet, little is known about associations between cardiovascular risk factors and cognition specifically post-arrest.

Fatigue has physical, emotional, behavioral and cognitive components [166]. It is a common phenomenon following OHCA, present in approximately 70% of survivors at six months and remaining in half of the survivors one year post-OHCA [100, 167]. This overwhelming feeling of tiredness and exhaustion can be considered as a symptom or a comorbidity of neurological disease and interferes with activities of daily living, has a negative impact on quality of life, and is a reason for early retirement [168]. The relationship between fatigue and domain-specific cognitive impairment following ABI is not extensively researched [169].

Worse cognitive function in general has, however, been associated with increased self-reported symptoms of anxiety, depression, and fatigue following OHCA [100, 155], although a smaller study did not find that cognitive function measured by memory performance predicted psychological wellbeing [170]. Besides, self-reported limitations in physical function in OHCA survivors appear related to cognitive impairment [171]. These studies mainly used performance-based screening measures. When investigating the broader effects of post-OHCA cognitive impairments, worse psychomotor function has been associated with worse physical health-related quality of life, whereas worse memory has been associated with worse mental health-related quality of life [172]. Depression and worse cognitive function predict lower participation following OHCA [100], and OHCA survivors with pronounced brain injury have decreased chances of return to work [173]. In essence, the interplay between cognition and associated factors should be investigated with more comprehensive data than earlier studies.

Cognitive recovery and rehabilitation

Rehabilitation frameworks

The ICF model

The International Classification of Functioning, Disability and Health (ICF) of the World Health Organization describes the impact on a health condition on functions, activities, and participation, as well as the interaction between health conditions, environmental factors, and personal factors [174]. This patient-centered biopsychosocial model has been used as a framework to describe outcome after cardiac arrest in a longitudinal study with survivors of cardiac arrest [167]. The ICF is often used in clinical rehabilitation services, such as cognitive rehabilitation for individuals with a cognitive impairment after an ABI.

Cognitive and neuropsychological rehabilitation

Cognitive rehabilitation is mostly concerned with psychoeducation, internal and/or external compensatory strategies rather than restoration of functions, aiming to reduce the impact of cognitive impairments and to improve overall well-being and daily functioning [175]. See Fig. 5 for a treatment planning decision tree within cognitive rehabilitation, which illustrates approaches, strategies, and techniques that are recommended depending on the patient's level of cognitive impairment and awareness thereof. The term cognitive rehabilitation is sometimes used interchangeably with neuropsychological rehabilitation, although the latter term is broader and integrates cognitive, emotional, social, and behavioral consequences of the brain injury [176]. Functions may improve due to spontaneous recovery but there is a growing evidence base that neuropsychological rehabilitation interventions promotes neuroplasticity [177]. Neuroplasticity is a driving force in recovery following brain injury and refers to the ability to adapt in response to stimuli via synaptic connections between neurons [178].

Non-pharmacological interventions to promote cognitive recovery

Identifying the need for interventions after cardiac arrest

Accurate and timely assessment is vital to identify the need for long-term interventions following OHCA [124]. In that respect, European guidelines recently recommended that functional assessments of physical and non-physical impairments are performed before hospital discharge to identify early rehabilitation needs and that referrals are sent to rehabilitation if necessary [54].

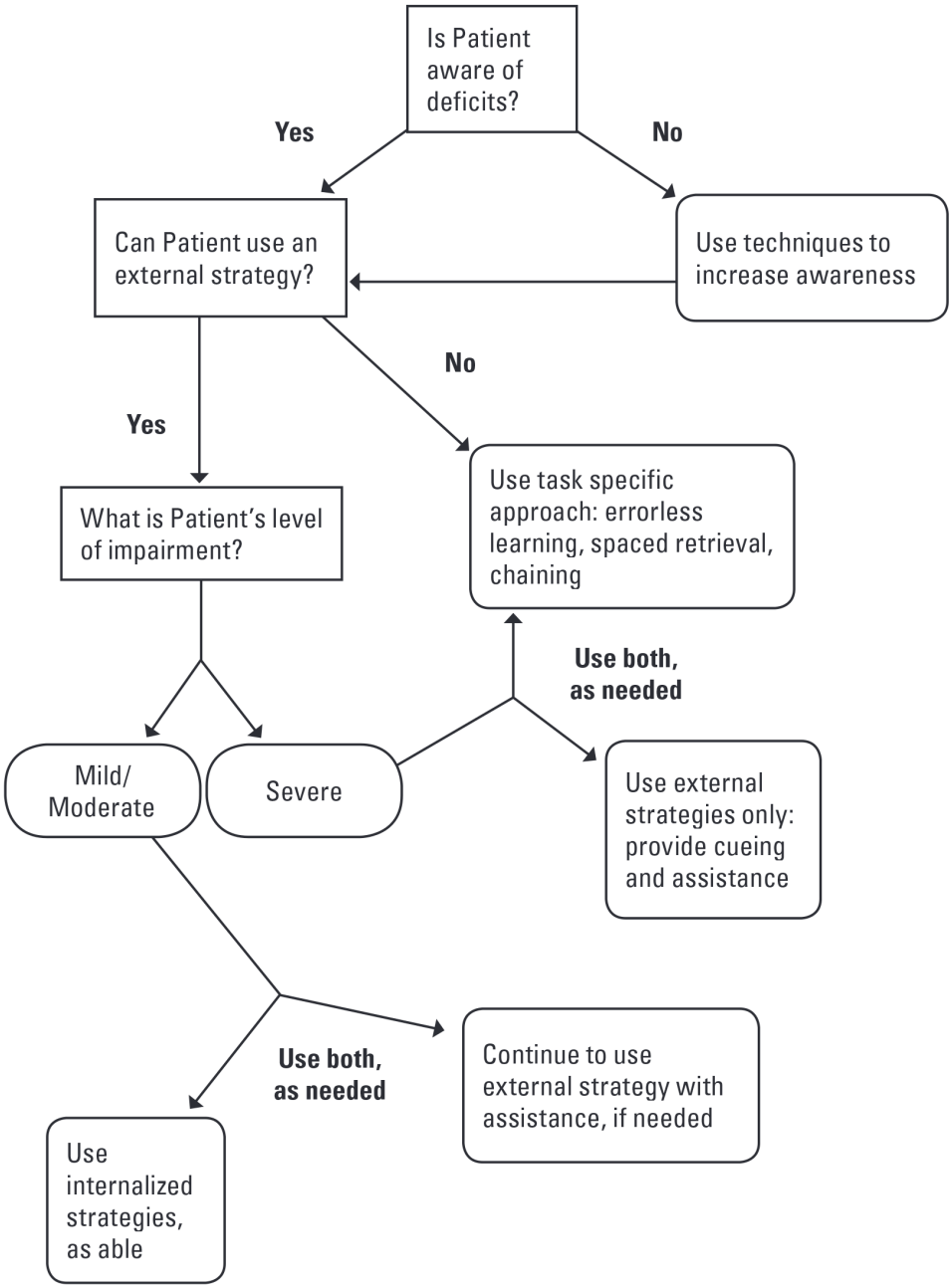

Fig. 5 Decision tree for treatment planning within clinical cognitive rehabilitation. Reproduced with permission from the Cognitive rehabilitation manual [179]. Copyright (2013) The American Congress of Rehabilitation Medicine.

Furthermore, a follow-up for all cardiac arrest survivors should be organized within three months after hospital discharge, including screening for cognitive problems, emotional problems and fatigue, and providing information and support for survivors and family members. In this way, patients with signs of impairment could be referred to a neuropsychologist or another specialist in cognitive rehabilitation within specialized care.

Promoting cognitive recovery after ABI

There is a large body of evidence to support the efficacy of cognitive rehabilitation after ABI [180], however no specific study on survivors of cardiac arrest. Intensive and early onset rehabilitation programs promote the functional recovery of patients with moderate to severe traumatic brain injury according to a meta-analysis [181]. A Cochrane review has reported strong evidence for the use of multidisciplinary milieu-oriented cognitive rehabilitation for adult of working age with severe ABI, in a therapeutic environment and involving a peer group of patients [182]. According to clinical recommendations in a systematic review of traumatic brain injury and stroke studies, post-acute comprehensive-holistic neuropsychological rehabilitation is effective and should be provided to reduce functional, cognitive, and psychosocial disability after traumatic and nontraumatic brain injuries [183].

Promoting cognitive recovery after cardiac arrest

The evidence of interventions to promote cognitive recovery is thinner after cardiac arrest, and primarily based on rehabilitation approaches used in other types of ABI [184, 185]. Yet, some of this evidence is based on studies with mixed cohorts which include small proportions of OHCA survivors. A cardiac arrest specific exception is a multicenter randomized controlled trial of a nurse-directed intervention that screened for cognitive problems, offered emotional support, and stimulated self-management [186]. No cognitive training was included in the intervention. The intervention group experienced improvement in overall emotional state and anxiety after one year but there was no significant difference regarding societal participation. At three months, more participants of the intervention group were back at work and the intervention was cost-effective [186, 187]. There are promising results from a similar pilot multidisciplinary intervention, in which self-reported health improved from hospital discharge to six months, however without including a control group [188]. Furthermore, seeing as cardiac arrest survivors may have both physical and neurological sequelae, cardiac arrest rehabilitation has been recommended to integrate cardiac and cognitive rehabilitation services [189]. This coordination between care paths is, nevertheless, absent in many health care systems and has not been formally evaluated. Studies that investigate how integration with available community outreach programs or participation in formal neuropsychological rehabilitation services affects cognitive recovery specifically for survivors of OHCA appear to be absent [190]. Additionally, the evidence for

pharmacologic interventions to improve cognitive outcome in clinical cardiac arrest studies is currently weak [191]. In order to design streamlined intervention studies following OHCA, more information is needed on the level of cognitive impairment, its consequences, and its relation to associated factors.

Psychometrics

Reliability and validity

Instruments that measure cognitive functioning should exhibit acceptable reliability, validity, and feasibility. The relationship between reliability and validity is illustrated in Fig. 6. There exist several reliability and validity models.

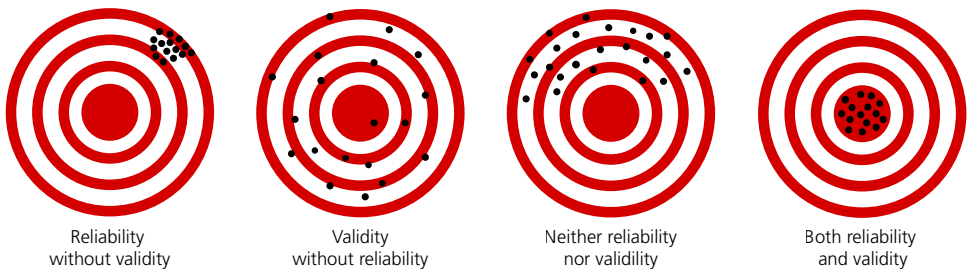

Fig. 6 Reliability and validity in a measurement concept illustrated as hits on a dart board. Consistent hits means high reliability. An average hit ratio close to the mean means high validity.

Reliability is the precision and consistency of an instrument over time [192], reflecting to which degree it is free from measurement error. Reliability concepts within this thesis focuses on consistency within the instrument (internal consistency reliability), but other reliability concepts are consistency over time (test-retest reliability), consistency across alternate forms (alternate form reliability), and consistency across raters (interrater reliability) [193].

In short, validity is the degree to which an instrument measures what it is intended to measure. Messick described two broad validity concepts, construct validity and utility [194]. Both validity concepts may be investigated with correlations and factor analysis (or principal component analysis). The construct validity can be defined as adequate *internal* instrument structure, including how well the individual items belong together. Here, the instrument should be representative of the intended measurement dimension or construct (i.e., memory tests should measure memory) – this is often assessed by comparing the new measure to already accepted measures, so called convergent validation. These measures must be selected with caution in an iterative process built

on hypothesis testing, so that correct inferences from the result are drawn [195]. On the other hand, utility emphasizes the *external* usage of the instrument in the community. Utility is closely related to the terms ecological and predictive validity; how well the instrument predicts real-life behavior. The utility depends upon if and how the instrument is used in an applied context (i.e., an instrument developed to measure cardiac arrest specific survivorship would have a lower utility if administered to a general population). Current assessment of validity integrates the traditional internal measurement-centered approach with a focus on the utility of the instrument [193].

Classification accuracy statistics

Instruments could be used to predict outcome such as cognitive impairment. When developing a new measure, the candidate instrument is often compared to the cut-off score of a highly accurate diagnostic instrument which is called a criterion or gold standard. Within neuropsychology, the gold standard test is not always 100% accurate, so any limitation in the accuracy need to be accounted for when interpreting classification accuracy statistics [193]. A high agreement between the gold standard and the candidate instrument is desirable. Agreements are referred to as *true positive* and *true negative* cases, with disagreements referring to *false positive* and *false negative* cases. The performance of a candidate instrument can be measured from Table 1.

Table 1. Classification/prediction accuracy of a candidate instrument in relation to a gold standard outcome.

	Candidate instrument outcome (predicted outcome)		
Gold standard instrument outcome ("actual" outcome)		**Positive**	**Negative**
	Positive	True positive	False negative
	Negative	False positive	True negative

Other metrics also arise from Table 1. Following the example with cognitive impairment, *sensitivity* is the percentage of people with cognitive impairment according to the gold standard who have a positive result on the candidate instrument (sensitivity = true positive / true positive + false negative). *Specificity* is the percentage of people without cognitive impairment according to the gold standard whose candidate instrument scores fall within the normal range (specificity = true negative / true negative + false positive).

Positive predictive value is the probability that the candidate instrument correctly identifies cognitive impairment. In other terms, the percentage of the times that true positive is the true value out of all the positive findings (positive predictive value = true positive / true positive + false positive). *Negative predictive value* is the probability that the candidate instrument correctly rules out cognitive impairment, that is, the

percentage of the times that true negative is the true value out of all the negative findings (negative predictive value = true negative / true negative + false negative).

Likelihood ratios combines sensitivity and specificity into a single metric of classification accuracy. A *positive likelihood ratio* tells us how much to increase the odds of cognitive impairment if the candidate instrument is positive (positive likelihood ratio = sensitivity / (1 - specificity)). A *negative likelihood ratio* tells us how much to decrease the odds if the candidate instrument is negative (negative likelihood ratio = (1 - sensitivity) / specificity). Ratios > 1 indicates an increased probability, while < 1 indicates a decreased probability. A ratio of 1 means that the candidate instrument approximation is random.

If the candidate instrument should be used to predict a dichotomous outcome such as cognitive impairment or not, the optimum cut-off score on the candidate instrument may be established by again dichotomizing the gold standard [196]. Cut-scores may be helpful, but categorical decisions within neuropsychology are rarely based on test performance alone, and the process by which cut-scores are determined must be done with care and be clearly documented [195]. A common method to determine cut-scores is *receiver operating characteristic* (ROC) analyses, which plot the proportion of true positives (sensitivity) on the Y-axis against the proportion of true negatives (1 - specificity) on the X-axis. See Fig. 7. The *area under the curve* (AUC) is the proportion of the entire sample correctly classified, that is, the overall accuracy of the test [193].

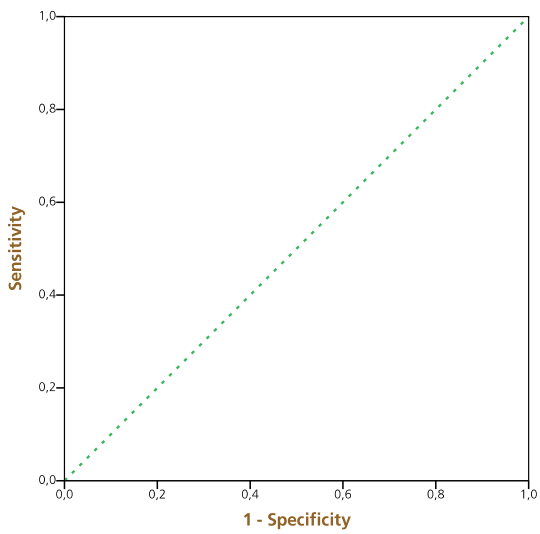

Fig. 7 An empty receiver operating characteristic plot. The candidate instrument (independent variable) can here be plotted against the cut-point of the gold standard instrument (dependent variable). The diagonal line represents the .5 area under the curve (AUC), a mere 50%, non-discriminatory chance that the candidate instrument categorizes correctly. The optimum cut-score may be in the upper left-hand corner of the plot (AUC = 1), minimizing the overall number of false positive and false negative cases. The closer to 1 the AUC is, the better discriminatory accuracy.

The agreement between two dichotomized instruments that measures the same or a similar construct can be investigated with kappa or percent agreement statistics. Cohen's *kappa* or the kappa coefficient is an extension of the distribution of positives and negatives. Kappa examines the proportion of positives and negatives in a two-by-two contingency table in relation to the proportion of scores in these cells which would be expected by chance [196]. Like most other correlation statistics, kappa ranges from -1 to +1. Negative values are unlikely and 0 represents agreement that can be expected from random chance. The closer the kappa value gets to 1, the better. *Percent agreement* instead examines the proportion of the two instruments that classifies in the same way. This metric is easily interpretable but does unlike kappa not correct for the proportion agreement expected by chance.

The normal distribution

The normal distribution operates with the expectation that the distribution of frequencies is continuous and shaped like the Gaussian bell curve. Namely, that most of the observations are clustered in the middle where the mean is, while observations are fewer on the tails. There exist several standardized scores based on the normal distribution with their own *M* and *SD*, such as *T*-scores (*M* = 50, *SD* = 10) or scaled scores (*M* = 10, *SD* = 3). These standardized scores are derived from normative data, usually from a general population. Standardized scores can be used to express results on, for instance, performance-based cognitive tests. Classifications on potential cognitive impairment are often based on such standardized scores, both in research and in clinical practice. To facilitate comparisons between tests, these scores may instead be presented corresponding with the standard normal distribution and expressed using *z*-scores (*M* = 0, *SD* = 1), see Fig. 8. A larger data set increases the possibility of achieving a normal distribution, so that statistically robust parametric tests may be conducted.

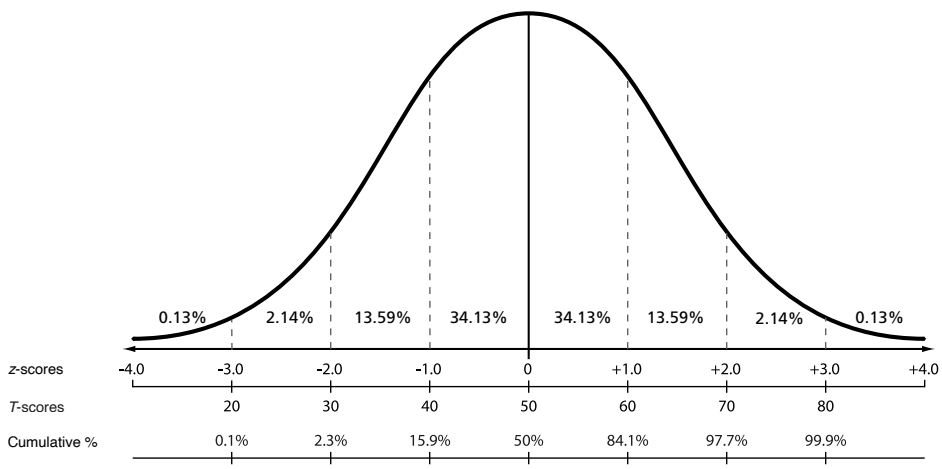

Fig. 8 The normal distribution expressed in *z*-scores, *T*-scores, and cumulative percentages.

Aims of the thesis

General aim

The overall goal of this thesis was to explore the extent of neurocognitive impairment following OHCA in the late recovery phase.

Brief description of aims in respective paper

I. To examine the psychometric properties of an observer-reported questionnaire modified for usage after cardiac arrest, the Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest (IQCODE-CA).

II. To explore associations between four outcome methods assessing neurocognitive outcome in the late recovery phase after OHCA and early hypoxic-ischemic brain injury assessed by the biomarker serum NFL, and to compare the agreement for the four outcome methods (clinician-reports, performance-based measures, patient-reports, and observer-reports).

III. To describe the rationale and design of the TTM2-trial neuropsychological sub-study, including a pre-specified plan of the analyses.

IV. To report initial results of the TTM2-trial neuropsychological sub-study: to describe cognitive impairment in OHCA survivors using neuropsychological tests, compare the cognitive performance to a matched cohort of participants following acute myocardial infarction (MI), and investigate the relationship between cognitive performance and the associated factors of emotional problems, fatigue, insomnia, and cardiovascular risk factors following OHCA.

Methods

Overview

A brief overview of the methods used in the papers of this thesis is found in Table 2. The papers in this thesis are based on patient cohorts included during different time periods, as illustrated in Fig. 9 and Fig. 10.

Table 2. Overview of methods used in the four papers included in this thesis.

Paper	I	II	III & IV
Design	Post-hoc analysis on a sub-study of an international multicenter trial	Exploratory post-hoc analysis of an international multicenter trial	Prospective case control sub-study of an international multicenter trial
Study context, ClinicalTrials.gov identifier	The TTM-trial cognitive sub-study, NCT01946932	The TTM-trial and its biobank, NCT01020916	The TTM2-trial neuropsychological sub-study, NCT03543371
Participants	268 individuals post-OHCA of presumed cardiac cause, managed with TTM at 33 °C or 36 °C	457 individuals post-OHCA of presumed cardiac cause, managed with TTM at 33 °C or 36 °C	• 108 individuals post-OHCA of presumed cardiac or unknown cause, managed with TTM at 33 °C or targeted normothermia with early treatment of fever (37.8 °C) • 92 controls post-acute MI without cardiac arrest
Time-point	About 6 months	About 6 months	About 7 months
Main instruments	IQCODE-CA, MMSE, RBMT, HADS	CPC, MMSE, IQCODE-CA, TSQ, serum NFL	Block Design, Matrix Reasoning, Digit Span, Vocabulary (of the WAIS-IV); Logical Memory, Spatial Span (of the WMS-III); Verbal Fluency, Color-Word Interference Test (of the D-KEFS); RAVLT, BVMT-R, TMT A & B, HADS, MFI-20, MISS
Main statistical analyses	Mann-Whitney *U*-test, Spearman's rho, exploratory factor analysis, ordinal alpha, ROC plots, linear regression, descriptive statistics	Spearman's rho, logistic regressions, ordinal regressions, ROC plots, kappa, percent agreement, descriptive statistics	Linear regressions, Mann-Whitney *U*-test, Fisher's exact test, Spearman's rho, descriptive statistics

TTM-trial, Target temperature management 33 °C versus 36 °C after out-of-hospital cardiac arrest trial; TTM2-trial, Targeted hypothermia versus targeted normothermia after out-of-hospital cardiac arrest trial; OHCA, out-of-hospital cardiac arrest; TTM, targeted temperature management; MI, myocardial infarction; IQCODE-CA, Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest; MMSE, Mini-Mental State Examination; RBMT, Rivermead Behavioural Memory Test; HADS, Hospital Anxiety and Depression Scale; CPC, Cerebral Performance Category; TSQ, Two Simple Questions; NFL, neurofilament light; WAIS-IV, Wechsler Adult Intelligence Scale – Fourth Edition; WMS-III, Wechsler Memory Scale – Third Edition; D-KEFS, Delis-Kaplan Executive Function System; RAVLT, Rey Auditory Verbal Learning Test; BVMT-R, Brief Visuospatial Memory Test-Revised; TMT Trail Making Test; MFI-20, Multidimensional Fatigue Inventory; MISS, Minimal Insomnia Symptom Scale; ROC, receiver-operating characteristic.

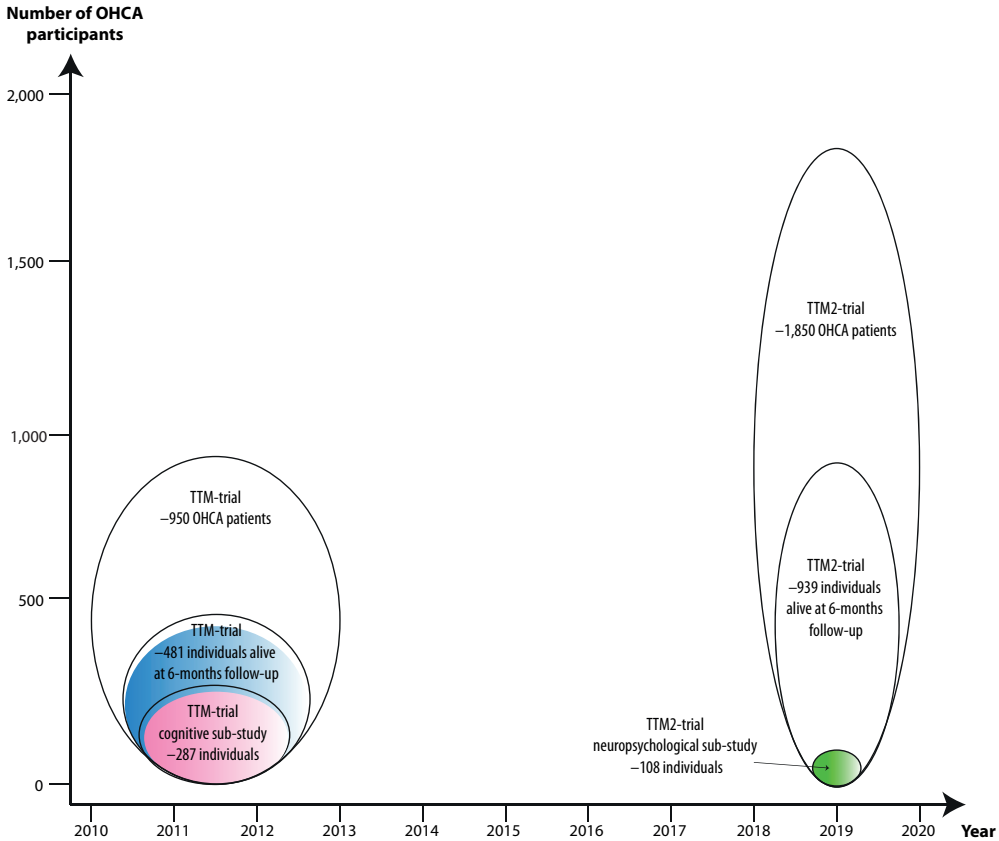

Fig. 9 Overview of the different clinical trials and sub-studies of relevance for this thesis, grouped by recruitment period in years and number of out-of-hospital cardiac arrest (OHCA) participants. The direct cohorts used for the papers in this thesis are colored and can be found in greater detail in Fig. 10. TTM-trial, Target temperature management 33 °C versus 36 °C after out-of-hospital cardiac arrest trial; TTM2-trial, Targeted hypothermia versus targeted normothermia after out-of-hospital cardiac arrest trial.

Validity of the IQCODE-CA (Paper I)

The TTM-trial

The TTM-trial was a prospective international multicenter randomized trial that randomized 950 comatose OHCA patients to TTM at either 33 °C or 36 °C [197]. The trial included patients from 36 intensive care units in Europe and Australia between 2010 and 2013.

Inclusion criteria were OHCA of a presumed cardiac cause, age ≥ 18 years, unconsciousness (a score of < 8 on the Glasgow Coma Scale) at hospital arrival, > 20 consecutive minutes of sustained ROSC. Exclusion criteria were > 240 minutes

between ROSC and screening, unwitnessed arrest with asystole as the initial rhythm, suspected or known stroke or intracranial hemorrhage, a body temperature < 30 °C, pregnancy, persistent cardiogenic chock despite medical interventions, and pre-existing neurologic disability [197].

The modified intention-to-treat cohort consisted of 939 patients. Surviving patients were invited to a face-to-face follow-up at 180 days (6 months), which if needed could be performed over telephone. The trial found no differences in all-cause mortality at 180 days or neurological function, as evaluated with the clinician-reports Cerebral Performance Category (CPC) and mRS at 180 days, between the two groups [42]. Health-related quality of life was overall good with no between-group differences, which also was the case on the cognitive screening measures Mini-Mental State Examination (MMSE), IQCODE-CA, and Two Simple Questions (TSQ) [198].

The TTM-trial cognitive sub-study

At the 180-days follow-up of the main TTM-trial, participants at 20 of 36 sites underwent cognitive tests within the cognitive sub-study, directly following the main trial outcome assessment protocol. The cognitive sub-study sites were located in Sweden, Denmark, the Netherlands, Italy, and the United Kingdom. A cohort of participants with STEMI but no cardiac arrest were recruited as a control group with an intended 2:1 ratio, and matched for age, sex, country, and time of hospitalization [199].

Surviving OHCA participants were grouped by temperature intervention, with 148 individuals included in the 33 °C group, 139 individuals included in the 36 °C group, and 119 individuals included in the STEMI control group. The TTM-trial cognitive sub-study detected no differences between the two OHCA groups on the Rivermead Behavioural Memory Test (RBMT), Frontal Assessment Battery, and Symbol Digit Modalities Test (SDMT). Cognitive impairment was common both in the OHCA groups and in the STEMI control group, with a significant difference found only on the SDMT that assessed functions related to attention/processing speed. OHCA participants performed worse than STEMI controls on the SDMT [200].

Participants

Eligible for Paper I were surviving OHCA participants in the TTM-trial cognitive sub-study, whose informants had completed the IQCODE-CA.

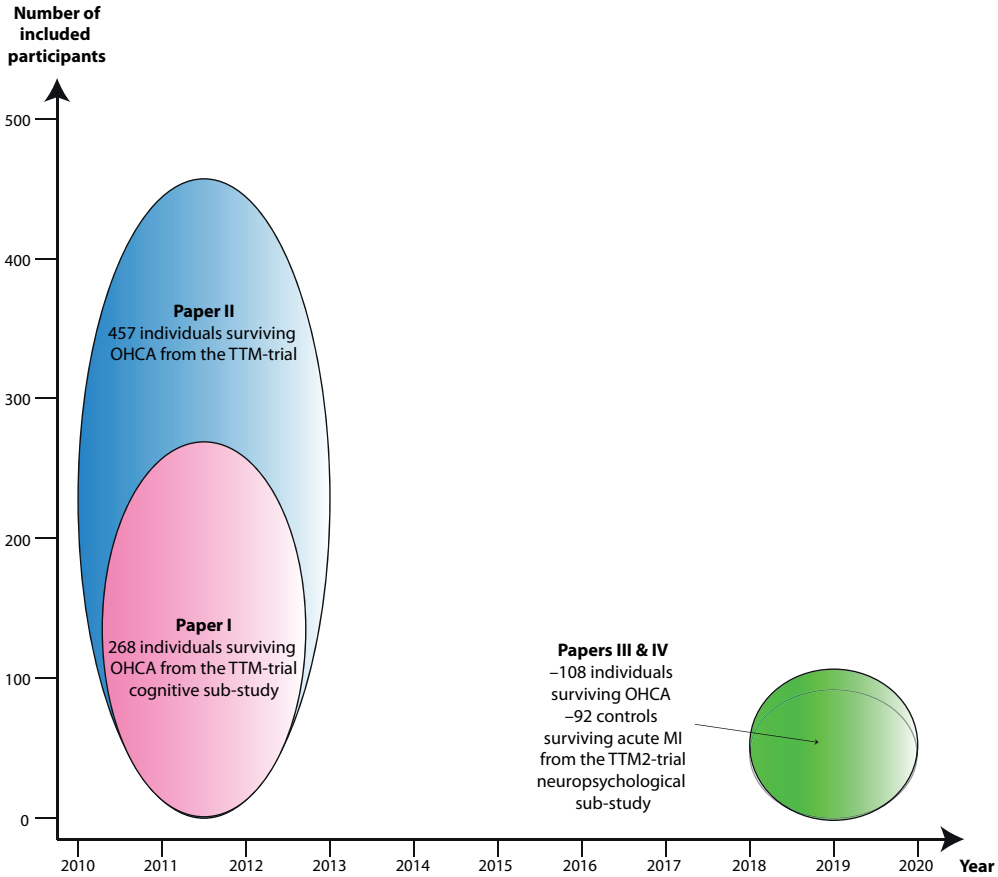

Fig. 10 Overview of the number of included participants and recruitment period in years for the papers in this thesis. OHCA, out-of-hospital cardiac arrest; TTM-trial, Target temperature management 33 °C versus 36 °C after out-of-hospital cardiac arrest trial; MI, myocardial infarction; TTM2-trial, Targeted hypothermia versus targeted normothermia after out-of-hospital cardiac arrest trial.

Instruments and outcome measures

Paper I aimed to evaluate the IQCODE-CA, and therefore this instrument was used as the independent variable. The performance-based MMSE and RBMT were used to investigate convergent validity. A patient-reported screening of emotional distress, the Hospital Anxiety and Depression Scale (HADS), was included since subjective cognitive complaints and emotional distress following ABI are related.

The IQCODE-CA

Designed as an observer-reported outcome screening measure on major neurocognitive disorders, the original Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) provides an appraisal of decline in everyday cognitive function over the

latest ten years [201]. This scale consists of 26 items each ranging from 1 ("much improved") to 5 ("much worse"), where 3 corresponds with "not much change". The items are totaled and divided by the number of completed items so that an index score from 1 to 5 can be provided. Suggestions on cut-scores for possible subtle cognitive decline have been 3.07, 3.15, and 3.19 in previous studies [202-204]. For the TTM-trial, a slightly modified version called the IQCODE-CA was utilized. Here, informants were asked to compare current cognitive function with pre-arrest cognitive function, rather than with cognitive function ten years ago. The IQCODE-CA has since been used in the TTM2-trial and two ongoing trials [205-207].

The MMSE

This 11-item cognitive screening measure was developed as a short tool to grade neurodegenerative disorders. Scores range from 0 to 30 with lower scores indicating greater cognitive impairment. There are several suggested cut-points for the MMSE; scores < 27 and < 21 have been proposed in the official MMSE manual for mild and moderate–severe cognitive impairment, respectively [208]. The MMSE has been repeatedly criticized for not adequately identifying mild neurocognitive decline [209].

The RBMT

The RBMT is an 11-subtest screening of impairment in everyday memory functions [210]. It was designed to detect memory problems that could hinder rehabilitation interventions for adults with ABI [211]. The instrument has a promising predictive validity, as it correlates moderately with activities of daily living and independence despite small-moderate sample sizes in the studies [212, 213]. It exhibits a ceiling effect and should therefore primarily be administered to individuals with suspected moderate to severe memory impairment [211]. More information about the internal consistency and test-retest reliability of the RBMT is needed [193].

The HADS

Perhaps the most widely used screening of emotional distress in research literature, the HADS consists of two conjoined 7-item subscales designed to indicate symptoms of depression and anxiety [214]. Each item ranges from 0 to 3, with higher total scores indicating more symptoms. The original authors advise that a score of 8–10 per sub-scale signals possible mood disorder and ≥ 11 signals probable mood disorder, but optimal cut-points vary across studies and values ≥ 8 are commonly recommended [215]. The HADS has been criticized for a too narrow focus on anhedonia in depression, a shared trait among medically ill patients who may not suffer from depression [216]. Evidence of the factor structure varies between studies, and it has been suggested that the HADS rather is an effective measure of general emotional distress [215, 217]. Its reliability for use after MI and cardiac diagnoses is acceptable [218, 219].

Statistical analyses

We investigated the data quality of the IQCODE-CA using the item and index score distribution and examined demographic relations with Mann-Whitney *U* tests and Spearman's rho. An exploratory factor analysis was performed, and a subsequent parallel analysis to determine the number of factors to retain from the factor analysis. Internal consistency was examined by an ordinal variant of Cronbach's alpha, called ordinal alpha. Ordinal alpha and a linear regression were performed to explore the feasibility of a 16-item Short IQCODE on cardiac arrest survivors. The AUC in ROC plots was used to identify optimal cut-scores on the IQCODE-CA, with the MMSE and RBMT as dependent variables.

NFL and neurocognitive function (Paper II)

Participants

Participants of the main TTM-trial who were alive at 180 days were included in Paper II. Additional inclusion criteria for Paper II were a completed CPC at 180 days and at least one of the following instruments: MMSE (administered face-to-face only), TSQ, and IQCODE-CA.

Instruments and outcome measures

Serum was sampled at 48 and 72 hours after ROSC, aliquoted, frozen to -80 °C, and stored at the Integrated BioBank of Luxembourg. After completion of the TTM-trial, NFL concentrations were measured at the neurochemistry laboratory in Mölndal, Sweden, using a homebrew kit on the Simoa HD-1 Analyzer (Quanterix). NFL data were used for the peak levels, that is, the highest values at 48 or 72 hours.

The instruments in Paper II were selected to represent the each of the four different outcome methods: clinician-reported, performance-based, patient-reported, and observer-reported outcome. We chose one instrument per outcome method to simplify the analyses.

- Clinician-reported outcome: CPC
- Performance-based outcome: MMSE
- Patient-reported outcome: TSQ
- Observer-reported outcome: IQCODE-CA

The CPC and TSQ are depicted in detail below, while the MMSE and IQCODE-CA have been accounted for when describing Paper I in this thesis.

The CPC

The CPC is the historical criterion or gold standard when classifying neurological status following cardiac arrest (Table 3) [220]. The five-level clinician-reported scale is a concise categorization of overall neurologic outcome including death. It has been criticized for lacking psychometric validation, for chunking several separate health and health-related domains into the same category, poor inter-rater reliability, and for exhibiting weak associations with measures of disability and quality of life [221, 222]. There exist modifications with promising psychometric properties [223, 224], but they were not used in Paper II. The original CPC is still the most widely used scale in studies on neurological prognosis after cardiac arrest [54].

Table 3. The five categories of the Cerebral Performance Category (CPC).

Category	Description
CPC 1	**Good cerebral performance.** Might have mild neurologic or psychologic deficit. Conscious, alert, able to work.
CPC 2	**Moderate cerebral disability.** Conscious, sufficient cerebral function for independent activities of daily life. Able to work in a sheltered environment.
CPC 3	**Severe cerebral disability.** Wide range of neurological conditions where the patient is dependent on others in activities in early life.
CPC 4	**Coma or unresponsive wakefulness syndrome/vegetative state.** Any degree of coma without the presence of all brain death criteria. No interaction with the environment. May have spontaneous eye-opening and sleep-wake cycles.
CPC 5	**(Brain) death.** Certified brain death or death by traditional criteria.

Although further losing in granularity, the scale can be dichotomized, usually into CPC 1–2 representing good outcome and CPC 3–5 representing poor outcome. When dichotomized here, we however mostly chose to dichotomize good outcome as CPC 1 only to increase sensitivity. A similar approach has been used in stroke trials with the mRS [225].

We included the CPC as the clinician-reported measure in favor of the mRS because the latter puts greater emphasis on physical abilities than the CPC, as used in the TTM-trial. The mRS also lacks the category coma or unresponsive wakefulness syndrome/vegetative state, and as such may not be able to differentiate between poorer neurocognitive outcomes.

The TSQ

This patient-reported outcome measure was developed as a simple and quick way to assess outcome reported by patients, which could make it suitable for large-scale trials

and telephone interviews [226]. The TSQ has been used to classify outcome in individuals surviving a stroke and has in these circumstances exhibited generally high sensitivity and specificity [227]. When used with survivors of an OHCA, the TSQ seemingly correlates well with the telephone based MMSE and a patient-reported quality of life measure [228], and it has been used in a few other studies [156]. Nevertheless, the overall psychometric evidence is limited due to a lack of studies that evaluates the instrument on an OHCA population. In Paper II, question 2 of the TSQ was used: "Do you feel that you have made a complete mental recovery after your heart arrest?" (yes/no).

Statistical analyses

We compared the association of the four different outcome instruments to peak serum NFL with Spearman's rho. Regression models (logistic and ordinal, depending on the data distribution of the instruments) were computed to control for potential covariates, all with $\log_{10}$-transformed NFL as predictor. ROC plots and AUC examination with NFL as the independent variable and dichotomized outcome instruments were used to compare the degree of predictability on NFL and the respective outcome instruments. Spearman's rho was utilized to test internal associations between the outcome instruments. Unweighted Cohen's kappa and percent agreement were calculated to investigate the strength of agreement between the instruments.

Neuropsychological function (Papers III and IV)

The TTM2-trial

The TTM2-trial was a prospective international multicenter randomized trial that included patients between 2018 and 2020 at 61 hospitals in Europe, Australia, New Zealand, and to a lesser extent, the United States. The trial randomized 1,900 comatose OHCA patients to either TTM at 33 °C ("hypothermia") or normothermia and early treatment of fever, with fever defined as ≥ 37.8 °C.

The TTM2-trial took a more pragmatic approach than the TTM-trial, allowing OHCA of a presumed cardiac cause or of an unknown cause as well. Other inclusion criteria were 20 minutes of sustained ROSC, unconsciousness (FOUR score motor response < 4 and not following verbal commands), eligibility for intensive care without restrictions, and ≤ 180 minutes between ROSC and screening. Exclusion criteria were unwitnessed arrest with asystole as the initial rhythm, intracranial hemorrhage, a body

temperature < 30 °C, pregnancy, extracorporeal membrane oxygenation, and chronic obstructive pulmonary disorder with home oxygen therapy prior to ROSC [229].

The intention-to-treat population consisted of 1,861 patients. The trial did not find any difference in all-cause mortality at 180 days or mRS ≥ 4 corresponding with a poor functional outcome at 180 days between the hypothermia and normothermia groups. Furthermore, overall health-related quality of life was similar in both groups, regardless of whether only surviving participants were evaluated or if the patients who died also were included in the analysis [44].

The TTM2-trial neuropsychological sub-study

At the main TTM2-trial follow-up at 180 days (6 months), participants at 8 of 61 sites in Sweden, Denmark, and the United Kingdom were invited to a separate examination at approximately 7 months. For participants that accepted the invitation, a standardized battery with neuropsychological tests of cognition was administered during the appointment and questionnaires were filled out prior to or after the visit. A cohort of participants with acute MI (STEMI and non-STEMI) were recruited as a matched control group. The eight participating sub-study sites were selected based on their availability of infrastructure and qualified study examiners, with an intention to recruit a sample of 100 patients per group. The same test battery and questionnaires were repeated 24 months post-cardiac event. The neuropsychological sub-study aimed to provide detailed and longitudinal information on cognitive impairment in OHCA survivors, compare the cognitive performance to a matched cohort of participants following acute MI, and investigate the relationship between cognitive performance and the associated factors of emotional problems, fatigue, insomnia, and cardiovascular risk factors following OHCA. The study also aimed to validate the main TTM2-trial neurocognitive screening.

Participants

Eligible for Paper IV were participants from the TTM2 sub-study sites, as described in Paper III. Additional sub-study exclusion criteria were ≥ 80 years of age, clinical major neurocognitive disorder diagnosis before the cardiac event, need of interpreter, active drug abuse, and a Clinical Frailty Index ≥ 8, indicating very severe frailty [230]. The MI controls were recruited with an intended 1:1 ratio and matched for time of cardiac event, sex, and age. One site per country was responsible for enrolment of MI controls for organizational purposes, but responsible sites were allowed to include MI controls outside their regular geographical area. Exclusion criteria for the MI controls were the same as for the OHCA survivors, with the addition that controls should not have suffered a cardiac arrest before or in connection with the MI.

Table 4. Neuropsychological tests of Papers III and IV, grouped by cognitive domain.

Cognitive domain	Cognitive functions	Test	Scores
Verbal	Verbal comprehension Concept verbalization Semantic memory retrieval	WAIS-IV Vocabulary	**Total score**
	Phonemic fluency Semantic memory retrieval Working memory capacity Processing speed	D-KEFS Verbal Fluency	**Letter fluency score, category fluency score**, category switching score, category switching accuracy, first interval, second interval, third interval, fourth interval, set-loss errors, repetition errors
Visual/constructive	Visuospatial organization Visuomotor speed	WAIS-IV Block Design	**Total score**, no time bonus score
	Non-verbal abstract reasoning Perceptual organization	WAIS-IV Matrix Reasoning	**Total score**
Working memory	Verbal short-term working memory Aspects of auditory attentional capacity	WAIS-IV Digit Span	**Total score**, digit span forwards score, digit span forwards longest, digit span backwards score, digit span backwards longest, digit span sequencing score, digit span sequencing longest
	Spatial working memory	WMS-III Spatial Span	**Total score**, spatial span forward, spatial span backward
Episodic memory	Verbal episodic list memory Attention Verbal recognition memory	RAVLT	**Total recall, delayed recall**, delayed recognition, trial 1, trial 2, trial 3, trial 4, trial 5, trial 6, trial 7
	Verbal episodic memory of prose passages Verbal learning	WMS-III Logical Memory	**Total score I, total score II**
	Visual episodic memory Visual learning Visual recognition memory	BVMT-R	**Total recall, delayed recall**, recognition discrimination index, trial 1, trial 2, trial 3, learning, percent retained, recognition hits, recognition false alarms
Processing speed	Visuomotor processing speed Attention	TMT A	**Score**
	Word naming speed Color naming speed	D-KEFS Color Word Interference Test	**Color naming, word reading**
Executive functions	Cognitive flexibility Working memory Visuomotor processing speed	TMT B	**Score**
	Inhibition of a dominant and automatic verbal response Sustained selective attention	D-KEFS Color Word Interference Test	**Inhibition, inhibition total errors**

WAIS-IV, Wechsler Adult Intelligence Scale – Fourth Edition [231]; D-KEFS, Delis-Kaplan Executive Function System [232]; WMS-III, Wechsler Memory Scale – Third Edition [233]; RAVLT, Rey Auditory Verbal Learning Test [234]; BVMT-R, Brief Visuospatial Memory Test-Revised [235]; TMT, Trail Making Test [236, 237].
Note. Scores used for computing composite *z*-scores per cognitive domain appear in bold.

Instruments and outcome measures

We used a comprehensive test battery with neuropsychological tests of cognition. Each test rendered a standardized score according to population norms which was converted to a *z*-score. Of all scores, 19 total scores were computed to a mean that formed the 6 neuropsychological composite scores based on the principal cognitive domain of each test. See Table 4 for an overview.

Before or after the visit, participants filled out questionnaires on self-reported symptoms as specified in Table 5. Cut-scores of ≥ 8 were used to describe possible clinical conditions on the HADS subscales.

Table 5. Self-reported symptom questionnaires of Papers III and IV.

Focus	Questionnaire	Subscales
Anxiety and depression symptom screening	HADS	HADS Anxiety HADS Depression
Fatigue	MFI-20	General fatigue Physical fatigue Reduced activity Reduced motivation Mental fatigue
Insomnia screening	MISS	n/a

HADS, Hospital Anxiety and Depression Scale [214]; MFI-20, Multidimensional Fatigue Inventory [238]; MISS, Minimal Insomnia Symptom Scale [239].

The MI controls answered questions about the cardiovascular risk factors hypertension (treatment yes/no) and diabetes (prevalence yes/no) at the time of examination. This information had already been collected as pre-arrest comorbidities from the OHCA survivors, as part of the TTM2-trial.

As with the other papers in this thesis, data were not analyzed based on temperature allocation. Instead, differences in outcome between the temperature groups was investigated within the main TTM2-trial with a larger number of participants. The outcome at 7 months is reported in Paper IV, as pre-specified in Paper III. The validation of the TTM2-trial neurocognitive screening and the 24-month outcome will be analyzed in later works.

Statistical analyses

Due to different distributions of the data, we described the results on the neuropsychological tests as means and standard deviations and the results on the questionnaires as medians and quartiles 1–3. Then the profiles of the included OHCA survivors with major impairment $z \leq -2$ in at least one of six neuropsychological composite scores were compared to the remaining included OHCA survivors, using

Mann-Whitney *U* tests and Fisher's exact test. The assumptions for linear regressions were met when comparing the results for each cognitive domain between OHCA survivors and MI controls. Regression analyses were performed in three steps with the respective cognitive domain as dependent variable and reported as the mean difference (MD) equal to the slope β: unadjusted regressions in step 1, adjusted for level of education and sex in step 2 as pre-specified in Paper III, and adjusted for level of education, sex, hypertension, diabetes, symptoms of anxiety, depression, fatigue, and insomnia in step 3. We examined the associations between hypertension, diabetes, symptoms of anxiety, depression, fatigue, insomnia, and neuropsychological composite scores with Spearman's rho. There were no substitutions of missing data.

Ethical considerations

The investigations in this thesis were all approved by ethical boards in each country according to local laws and regulations. The participants received written and oral information, and the included participants of all studies in this thesis all gave written informed consent, with separate consent waivers for the TTM2-trial neuropsychological sub-study. Good clinical practice offices monitored the TTM-trial and the TTM2-trial.

All procedures complied with the Helsinki declaration, published by the World Medical Association and revised in 2013 [240]. Ethical considerations are imperative when treating patients in an intensive care setting, where patients cannot consent to the current care or to participate in clinical trials. In cases when further resuscitation attempts are considered futile, WLST should be based on reliable and standardized multimodal neuroprognostication methods. Worth noting is that the acceptance for this process differs between countries and may be influenced by socio-cultural norms and ethnicity [241]. The initiation of end-of-life care is widely considered acceptable in most countries with sites that participated in TTM-trial and TTM2-trial, and in all countries with TTM2-trial neuropsychological sub-study sites. From an ethical perspective, not practicing WLST is entailed with survival, a core value of all healthcare. Still, prolonged unresponsive wakefulness syndrome after OHCA is uncommon in northern Europe but more frequent in countries where WLST is not widely practiced [242]. Patients with unresponsive wakefulness syndrome do not show any normal brain activity and the longer the syndrome lasts, the less likely is it that the patients recover consciousness. That is, survival aside, there is a detrimental impact on functional status and quality of life for these patients.

Participants in the TTM2-trial neuropsychological sub-study actively consented to partake in the sub-study. They did not receive any economic compensation except an optional travel reimbursement. The participants were offered oral feedback on the

outcome of the neuropsychological examination at the end of the visit, or shortly after the visit by telephone. There was a predicted minor risk that the possible information on cognitive impairment would be experienced as cumbersome. The examiners were instructed to carry through the feedback with respect for the participants' wishes and to give shorter emotional support directly after the examination at signs of discomfort. Examiners were all psychologists or psychologist students under supervision, and thus had formal training to answer queries on psychometrics, cognition, and mood disorders. If results from the examination indicated cognitive impairment or emotional problems, and the participant gave their consent, the results were abbreviated and sent as a referral to their general practitioner, their primary care center, or to a specialized neurorehabilitation facility. We did this to facilitate support and timely management of cognitive impairment, emotional problems, and fatigue. Early detection has been proven important when related to OHCA, as mentioned in the section on Cognitive recovery and rehabilitation, and when related to neurocognitive disorders [186, 243].

Results

Validity of the IQCODE-CA (Paper I)

Of 287 included participants in the TTM-trial cognitive sub-study, 268 were included in Paper I. The median index score of the IQCODE-CA was 3.08 (Fig. 11). The analyses revealed no statistically significant relations between the IQCODE-CA and sex (p = .64), education (p = .36) or age (p = .97).

The parallel analysis detected an eigenvalue of 11.3 on the first factor and 0.8 on the second, indicating that the IQCODE-CA measures one underlying dimension,

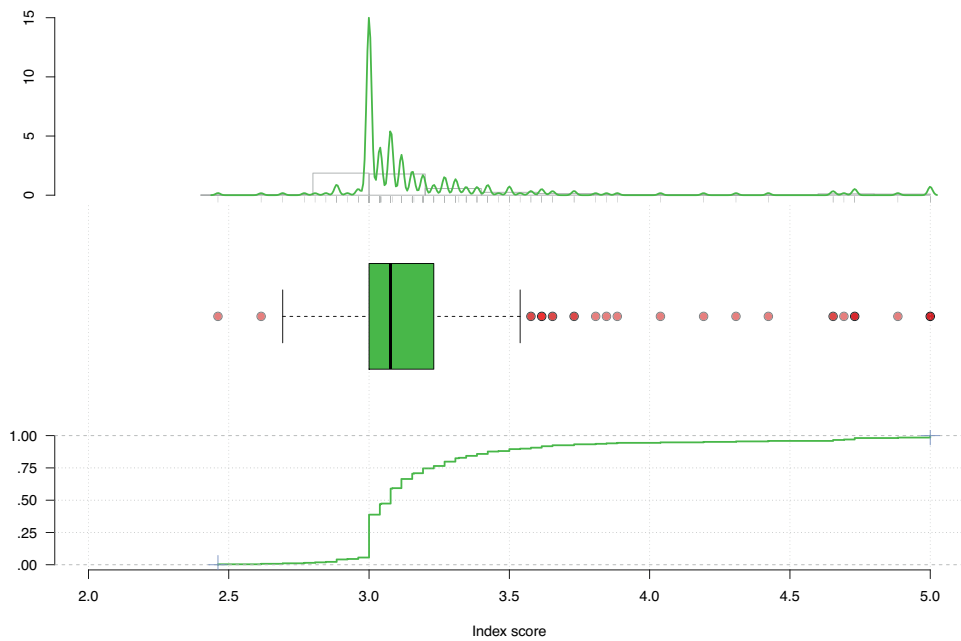

Fig. 11 Histogram, boxplot, and empirical cumulative distribution for the Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest (IQCODE-CA) index score. The box in the boxplot is the interquartile range, with the left end of the box being quartile 1 (3.00), the middle line the median (3.08), and the right end of the box quartile 3 (3.23). The end of the whiskers show the most extreme data points that are no more than 1.5 × the interquartile range from quartile 1/quartile 3 (2.69; 3.54). Outliers beyond the whiskers are individually plotted as red dots (*Min–Max* = 2.46–5.00).

global cognitive decline. The internal consistency reliability of the IQCODE-CA was high (α = .95). The 16 items in the Short IQCODE predicted the outcome on the IQCODE-CA to a large extent (R^2 = .965; p < .001), with retained internal consistency (α = .94).

The IQCODE-CA had a small negative association with the MMSE (r_s = -.29; p < .01) and the RBMT (r_s = -.29; p < .01), that is, worse MMSE and RBMT results correlated slightly with worse IQCODE-CA ratings. There was a small positive association with the HADS anxiety subscale (r_s = .29; p < .01) and a moderate positive association with the depression subscale (r_s = .38; p < .01), that is, more anxiety and depression symptoms correlated with worse IQCODE-CA ratings.

In the ROC curve analysis of the IQCODE-CA, the AUC ratio ranged from fair to good (.72–.81; Fig. 12). An IQCODE-CA index score of 3.04 was indicated as a sensitive cut-off for indicated cognitive decline when using an MMSE score < 27 and a RBMT profile score < 17. This cut-score was considered optimal for the IQCODE-CA, since the RBMT and MMSE scores in question are intended to identify mild–moderate cognitive decline. Using this score, 53% of the survivors had indicated global cognitive decline according to the informants.

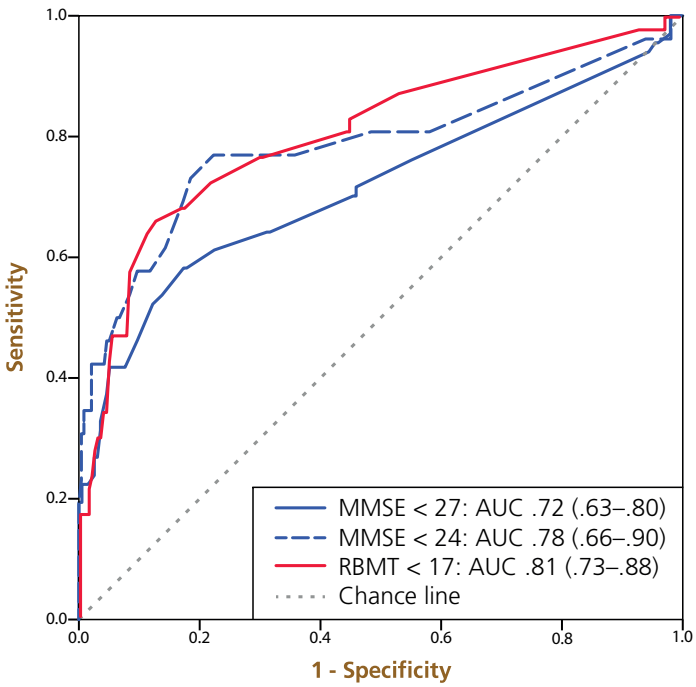

Fig. 12 Receiver-operating characteristics curves for the Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest (IQCODE-CA) as independent variable, in comparison to Mini Mental State Examination (MMSE) scores < 27 and < 24 respectively, as well as Rivermead Behavioural Memory Test (RBMT) scores < 17. Area under the curve (AUC) ratios are presented with 95% confidence intervals in parentheses.

NFL and neurocognitive function (Paper II)

Of 486 surviving participants in the TTM-trial at 180 days post-arrest, 457 were included in Paper II. Of these 457 participants, 384 had serum NFL analyzed at least once.

Serum NFL had small–moderate associations with the outcome instruments. NFL was most associated with the clinician-reported CPC (r_s = .41, 95% CI [.32, .49]) and least with the patient-reported TSQ (r_s = -.16, 95% CI [-.26, -.05]; Fig. 13).

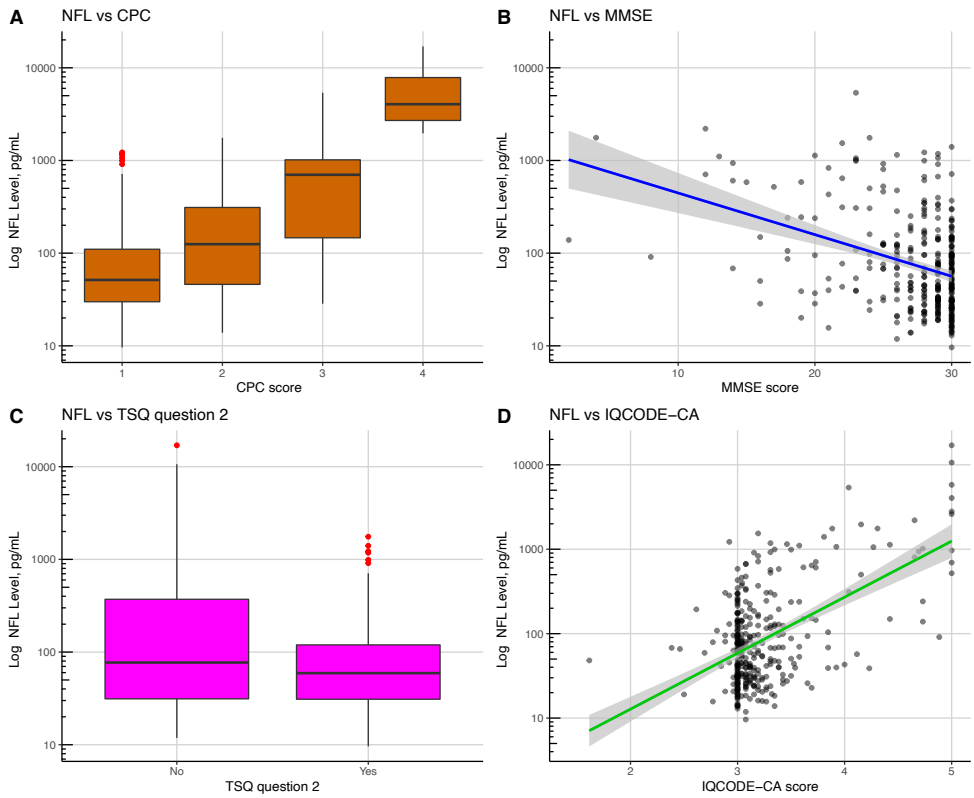

Fig. 13 Boxplots with outliers individually plotted as red dots (A, C), and scatter plots with regression lines and 95% confidence intervals in gray (B, D) for $\log_{10}$-transformed serum neurofilament light (NFL) peak levels at 48 or 72 h post-arrest, compared to the following outcome instruments at 180 days post-arrest. **A:** Cerebral Performance Category (CPC) 1–4. **B:** Mini Mental State Examination (MMSE) 0–30. **C:** Two Simple Questions (TSQ) question 2. **D:** Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest (IQCODE-CA) 1–5.

In unadjusted and age-adjusted regression models, NFL levels were significant in relation to the outcome instruments. Older participants had poorer MMSE and TSQ results and worse outcome on the CPC. In regression models adjusted for demographics and risk factors, the relationship between NFL and TSQ was no longer statistically significant. NFL levels remained significant in relation to the other outcome instruments. Older participants had worse IQCODE-CA results. Participants with > 12 years of education performed better on the MMSE than those with less education. Previous acute MI, ischemic heart disease, and/or coronary artery bypass grafting was associated with worse MMSE results. Lower vitality scores were associated with poorer CPC and IQCODE-CA results, whilst lower mental health scores were associated with worse MMSE, TSQ, and IQCODE-CA results.

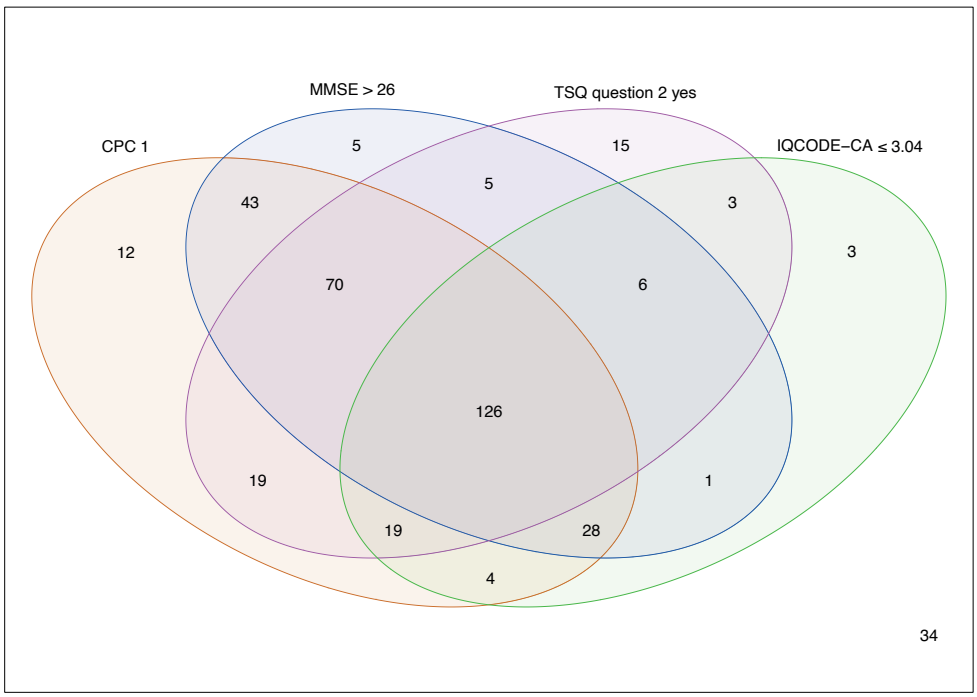

Fig. 14 Venn diagram of the number of participants with no–mild brain injury at 180 days post-arrest, according to the following criteria: Cerebral Performance Category (CPC) 1, Mini Mental State Examination (MMSE) > 26, Two Simple Questions (TSQ) question 2 yes, and Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest (IQCODE-CA) ≤ 3.04. Each instrument is represented by a circle; numbers in one circle represents the number of participants reaching a single criterion, for example, 12 participants had a CPC 1 score but did not meet the criteria for no–mild brain injury on the other outcome instruments. Numbers in overlapping circles represent the intersection between instruments, for example, 126 participants met the criteria for no–mild brain injury on all four outcome instruments. Alive and included participants not meeting criteria for no–mild brain injury on any of the four outcome instruments are presented outside the circles, *n* = 34. Only participants with results on all four outcome methods could be included in this diagram (*n* = 393).

AUCs for serum NFL to predict results on the dichotomized outcome instruments representing no–mild brain injury ranged from failed (TSQ: .59, 95% CI [.53, .65]) to fair (CPC 1: .78, 95% CI [.71, .85]). When instead using alternate, more permissive dichotomizations on the outcome instruments representing no–moderate brain injury, NFL was a stronger predictor (CPC 1–2: .90, 95% CI [.83, .98]).

Out of the outcome instruments, the IQCODE-CA indicated most cognitive problems (52%). The CPC indicated the least number of problems (CPC 2–4: 21%), which further decreased with the alternate dichotomization (CPC 3–4: 8%).

On the internal associations between the continuous outcome instruments, there were strong associations when comparing the CPC with the MMSE (r_s = -.53, 95% CI [-.59, -.44]) and the IQCODE-CA (r_s = .50, 95% CI [.41, .57]), and a moderate association between the CPC and the TSQ (r_s = -.33, 95% CI [-.42, -.22]). The association between the TSQ and the MMSE was small (r_s = .19, 95% CI [.06, .28]). Visualizations of the patterns of the dichotomized outcome instruments representing no–mild brain injury can be found in Fig. 14 and Fig. 15.

Moderate agreement was found between the CPC and the MMSE (κ = .50, 95% CI [.40, .60]), other agreements were fair.

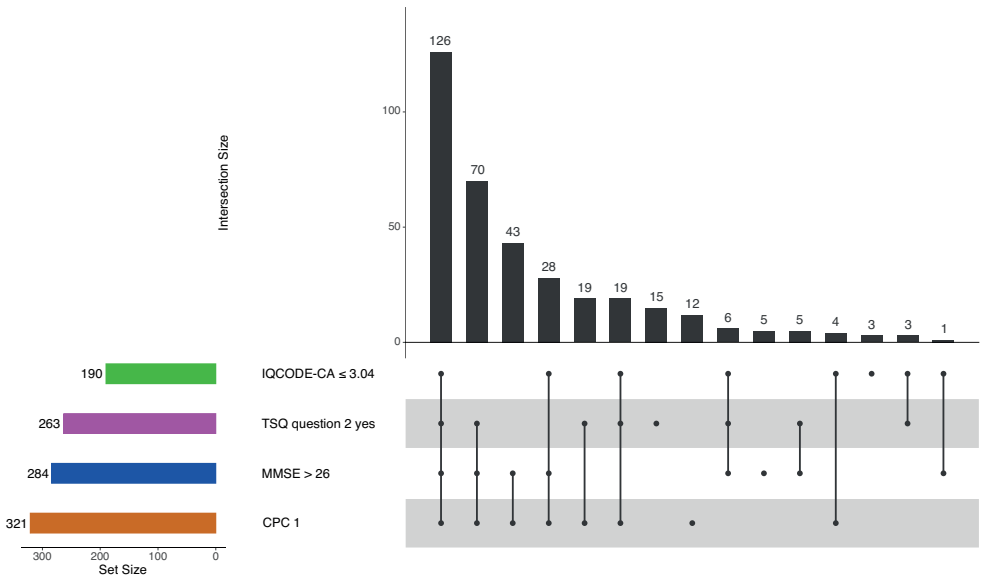

Fig. 15 Upset plot of the number of participants with no–mild brain injury at 180 days post-arrest, according to the following criteria: Cerebral Performance Category (CPC) 1, Mini Mental State Examination (MMSE) > 26, Two Simple Questions (TSQ) question 2 yes, and Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest (IQCODE-CA) ≤ 3.04 at 180 days post-arrest. Only participants with all four outcome methods reported *and* fulfilling at least one of the criteria for no–mild brain injury could be included in this plot (n = 359).

Neuropsychological function (Papers III and IV)

At 180 days post-arrest, there were 939 surviving participants in the TTM2-trial follow-up, whereof 230 were survivors at the 8 sub-study sites. Of those, 184 were eligible for participation in the neuropsychological sub-study and 108 were included in Paper IV. The matched control group consisted of 92 MI controls. The number of included participants per sites can be seen in Fig. 16. When comparing the 939 TTM2-trial survivors at all sites with the 108 OHCA survivors included in Paper IV, the median age was 60 vs 62, 84% vs 88% were men, 33% vs 38% had > 12 years of formal education, and 41% vs 34% scored < 26 on the MoCA, indicating cognitive impairment.

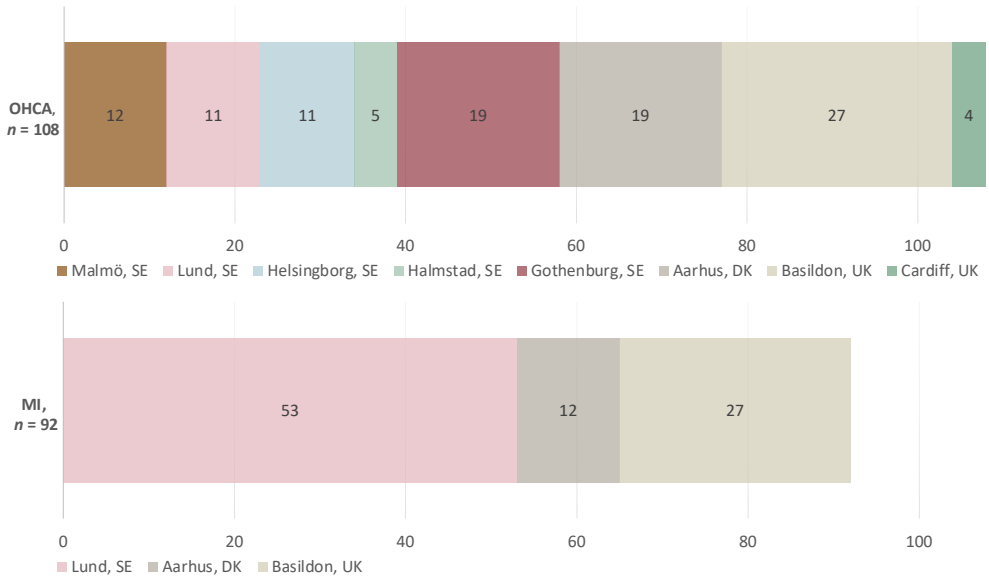

Fig. 16 Number of included out-of-hospital cardiac arrest (OHCA) survivors and myocardial infarction (MI) controls per sub-study sites in Sweden (SE), Denmark (DK), and the United Kingdom (UK).

On the neuropsychological tests of cognition, a similar amount of OHCA survivors and MI controls had scores indicating at least borderline–mild impairment at $z \leq -1$ in one single composite score (17% vs 21%). However, more OHCA survivors than MI controls (29% vs 16%) performed equivalent to at least borderline–mild impairment on two or more of the composite scores. Major cognitive impairment at $z \leq -2$ in one or more composite scores was more common among OHCA survivors (14%) than MI controls (4%).

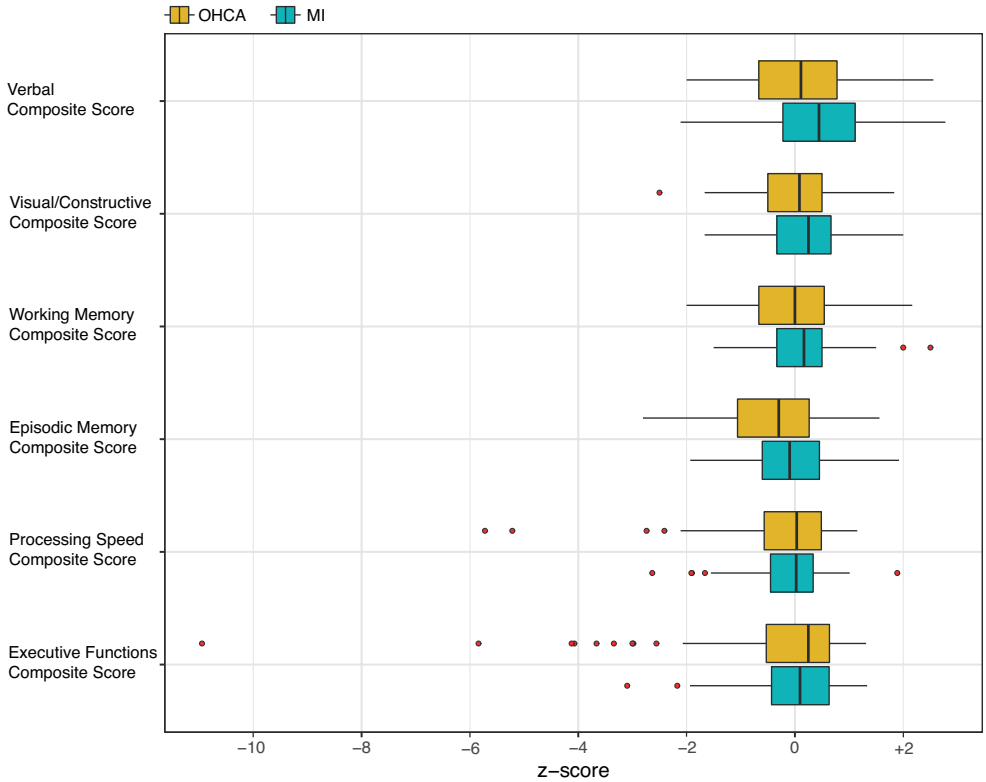

Fig. 17 Boxplots for the neuropsychological composite *z*-scores (normative *M* = 0, *SD* = 1) per out-of-hospital cardiac arrest (OHCA) survivors and myocardial infarction (MI) controls, with outliers individually plotted as red dots.

The largest proportion of composite scores indicating at least borderline–mild impairment was found in episodic memory (OHCA: 27%; MI: 13%) and executive functions (OHCA: 21%; MI: 11%), with outliers in the lower span of the result distribution in processing speed as well (OHCA: 13%; MI: 13%); details in Fig. 17.

Included OHCA survivors with major cognitive impairment (n = 15, 14%) had significantly higher rates of diabetes, lower rates of bystander-CPR, longer intensive care unit and hospital stay compared to the remaining included 93 OHCA survivors. At the time of examination, OHCA survivors with major cognitive impairment reported more symptoms of depression and fatigue, and were more frequently treated with psychotropic drugs.

When comparing the results on the neuropsychological tests between OHCA survivors and MI controls, OHCA survivors performed significantly worse in episodic memory on the unadjusted regression models in step 1. On the pre-specified regression models adjusted for educational attainment and sex in step 2, OHCA survivors retained worse performance than MI controls in episodic memory (MD = -0.37, 95% CI

[-0.61, -0.12]), with significantly worse performance in verbal (MD = -0.34, 95% CI [-0.62, -0.07]) and visual/constructive functions (MD = -0.26, 95% CI [-0.47, -0.04]) as well. When additionally adjusting for symptoms of hypertension, diabetes, anxiety, depression, fatigue, and insomnia in step 3, processing speed (MD = -0.41, 95% CI [-0.74, -0.09]) and executive functions (MD = -0.69, 95% CI [-1.13, -0.24]) were also worse following OHCA. Thus, our hypothesis that OHCA survivors would perform worse than MI controls was demonstrated.

The proportion of results indicating possible anxiety (OHCA = 21%, MI = 26%) and depression (OHCA = 15%, MI = 17%) were similar between groups. Results on the questionnaires can be found in Table 6.

Table 6. Results on self-reported symptom questionnaires.

	OHCA (n = 108)		MI (n = 92)	
	Median (Q_1–Q_3)	*Min–Max*	Median (Q_1–Q_3)	*Min–Max*
HADS Anxiety Subscale (*Min–Max* = 0–21)	3 (1–6)	0–18	4 (2–7)	0–18
HADS Depression Subscale (*Min–Max* = 0–21)	2 (1–4)	0–14	2 (1–6)	0–13
MFI-20 General Fatigue Subscale (*Min–Max* = 4–20)	10 (8–13)	4–20	11 (8–15)	4–19
MFI-20 Physical Fatigue Subscale (*Min–Max* = 4–20)	11 (7–14)	4–20	10 (8–14)	4–20
MFI-20 Reduced Activity Subscale (*Min–Max* = 4–20)	10 (6–13)	4–20	9 (7–13)	4–20
MFI-20 Reduced Motivation Subscale (*Min–Max* = 4–20)	8 (6–11)	4–20	9 (6–12)	4–17
MFI-20 Mental Fatigue Subscale (*Min–Max* = 4–20)	8 (4–10)	4–18	8 (4–11)	4–19
MISS (*Min–Max* = 0–12)	3 (1–5)	0–12	4 (2–6)	0–12

OHCA, out-of-hospital cardiac arrest; MI, myocardial infarction; Q_1–Q_3, quartile 1 to quartile 3; HADS, Hospital Anxiety and Depression Scale; MFI-20, Multidimensional Fatigue Inventory; MISS, Minimal Insomnia Symptom Scale.
Notes: Numeric low scores represent fewer symptoms on all questionnaires. Number of completed questionnaires (OHCA/MI): HADS, n = 107/91; MFI, n = 105/90; MISS, n = 107/91.

Amongst OHCA survivors, depressive symptoms were associated with worse executive functions (r_s = -.37, p < .001) and worse processing speed (r_s = -.27, p = .01). Anxiety symptoms (r_s = -.21, p = .01) and general fatigue (r_s = -.24, p = .01) were associated with worse executive functions. Mental fatigue was associated with worse episodic memory (r_s = -.21, p = .03) and executive functions (r_s = -.25, p = .01). Physical fatigue was associated with worse processing speed (r_s = -.26, p = .01) and executive functions (r_s = -.24, p = .01). Diabetes was associated with worse processing speed (r_s = -.20, p = .03), visual/constructive (r_s = -.29, p < .001) and executive functions (r_s = -.25, p = .02). Hypertension and insomnia were not significantly associated with neuropsychological test performance.

Discussion

The overall aim of the current thesis was to explore the extent of neurocognitive impairment following OHCA in the late recovery phase. In the first part of this section, I will discuss this overall aim based on the results from Paper IV. Since all papers of this thesis describe neurocognitive outcome reported by four different methods (performance-based measures, clinician-reports, patient-reports, and observer-reports), the second part of the discussion will assess pros and cons of each method, intertwined with interpretations of all papers included in the thesis. This will be followed by a discussion on the results of the thesis in relation to cognition and biomarkers, brain structures, neurorehabilitation, and general strengths and limitations.

Understanding the extent of cognitive impairment

Prevalence of cognitive impairment

A main result of Paper IV was that 29% of the included OHCA survivors had at least borderline–mild impairment on two or more of the neuropsychological composite scores. Major impairment in at least one composite score was observed in 14% of the OHCA survivors. Based on these results, the extent of cognitive impairment in the late recovery phase appears generally mild, and it is imperative to consider that a majority of the surviving OHCA participants performed without cognitive impairment in the neuropsychological assessment. Our findings are coherent with the broad 6–100% impairment range that has been previously reported, however somewhat lower than earlier high-quality studies estimates of 42–60% [127]. This minor discrepancy could at least partly be understood in consideration of the vast number of measures used to assess cognitive function following OHCA; the latest systematic review listed over 50 different measures with varying sensitivity [131]. The instruments that were selected for Paper IV were standardized and exhibited psychometrically robust norms. The granularity of our data would imply that the proportions reported in Paper IV are accurate, at least regarding the included participants.

Nonetheless, OHCA survivors with cognitive impairment may be slightly underrepresented in Paper IV, as a consequence of fewer included survivors having

indicated cognitive impairment on the MoCA in Paper IV than all survivors of the TTM2-trial. Especially individuals with major cognitive impairment and pronounced hypoxic-ischemic brain injury may have experienced a comprehensive neuropsychological examination as a too heavy burden.

Several other methodological aspects could explain why reported proportions of post-OHCA cognitive impairment differ between studies. The assessment points are diverse and higher proportions of impairment could be expected in the first weeks after OHCA, rather than the results we reported in Paper IV which could be mitigated by cognitive recovery.

There exist various cut-offs to classify scores as cognitive impairment, which may also account for the diverging results. Some works have utilized a criterion of $z \leq -1$ [244], and others $z \leq -1.50$ [135, 245]; there are examples of $z \leq -1.65$ [144], and $z \leq -2$ as well [139]. This is a trade-off between sensitivity and specificity. There are examples of studies that have used additional criteria, such as requiring more than one test result $z \leq -1$ to indicate impairment [246]. A methodological draw-back of this procedure is that the expected prevalence of cognitive impairment in the normal population is unclear due to multiple comparisons, with unclear interrelatedness between the tests or cognitive domains. Still, we pragmatically adapted this procedure in Paper IV to avoid measurement noise.

Cognitive function per cognitive domains

The results from Paper IV again confirmed that cognitive impairments in survivors of OHCA was most frequently observed in the episodic memory, executive functions, and processing speed domains. Contrastingly, impairments in working memory were fairly uncommon and followed the presumed test score distribution according to population norms. This underscores the need to differ between different memory processes in neuropsychological assessments of OHCA survivors. Verbal as well as spatial encoding and retrieval of novel lengthy information sequences, processes that load on episodic memory, appear to be more frequently impaired than the mental manipulation processes of the working memory.

The theory that there is a bimodal pattern of post-OHCA cognitive impairment (i.e., either "only" impairments in memory, processing speed, and executive functions *or* significant deficits in all cognitive domains) was not corroborated by the results of Paper IV. The entire range of the six assessed cognitive domains was represented among the OHCA survivors based on our $z \leq -1$ criterion, although impairments in multiple domains were rarer than impairments in one domain alone. We found a similar but not as pronounced pattern when investigating the distribution of individuals per numbers of impaired cognitive domains according to the $z \leq -2$ criterion.

Assessing each neurocognitive outcome method

Performance-based measures

Performance-based screening measures are, because of their brevity, suited for bedside use, primary care settings or clinical trials. Papers I and II of this thesis used the MMSE, which today has been largely replaced with the MoCA following cardiac arrest. The MoCA's sensitivity to OHCA-associated cognitive impairment is promising according to a recent study [116], and our performance-based screening results may have indicated a greater proportion of individuals with cognitive impairment if we would have used the MoCA instead.

Detailed cognitive assessments with neuropsychological tests are seldom specific for a disorder but should instead exhibit acceptable sensitivity and specificity for cognitive functions. As with screening measures, education has an effect on most neuropsychological tests, where low premorbid capacities may be misattributed to cognitive impairment [117]. Furthermore, as observed in Paper IV, worse cognitive performance on tests can be associated with emotional problems and fatigue following OHCA. A deduction from Paper IV on this matter is that test results should be interpreted with some caution if emotional problems and fatigue are indicated, since results may not reflect the full cognitive capacity of these individuals (nevertheless, these results would be very relevant when not primarily investigating cognitive functions but the impact off all factors on everyday life) [247]. A clinical neuropsychological evaluation must therefore integrate the test data with personal history and behavioral observations into a relevant description of the patient [248], and use a differential diagnosis approach. A pitfall associated with most performance-based measures of cognition, including neuropsychological tests, is that they measure a combination of cognitive functions [249]. Performance-based measures are in general highly correlated with each other, and little variation between scores is specific to a single instrument [250]. Neuropsychological test profiles may however be associated with a particular disorder in clinical groups, for example, memory, attention/processing speed, and executive functions are frequently reported as impaired among OHCA survivors [127, 131]. In Paper IV, we observed a discrepancy in the impairment frequency between two tests within the same cognitive domain in the OHCA cohort. Together with our choice to combine test to composite scores, this may be an effect of the task impurity problem, according to which neuropsychological tasks call for interaction between different cognitive processes [251]. The overlap between sub-components of the same cognitive domain, or even between several cognitive domains, when utilizing a single test needs to be considered in research and clinical practice [252]. Besides, as indicated by the attrition rate in Paper IV, detailed neuropsychological assessment may not be

optimal for individuals with major cognitive impairment or those who experience it as burdensome.

Functional cognitive assessments that are designed to measure real life situations, activity or participation were not utilized in this thesis. A multidimensional measurement of cognitive functioning with both traditional tests and tests that measure cognition in everyday life has lately been recommended following ABI [253]. In large cardiac arrest trials, there are logistical and cost issues that could make all detailed cognitive assessment lesser suitable than screening tests [254].

Clinician-reports

Clinician-reports play a large role in clinical trials. If administered in a standardized manner, clinician-reports should weigh in all available behavioral data in the scoring. This is a clear benefit of clinician-reports. The well-established CPC lacks standardization in its original form, which complicates scoring and subsequent interpretation. Two studies have reported that the MMSE and a modified version of The Telephone Interview for Cognitive Status were more sensitive to post-arrest cognitive impairment than the CPC [255, 256]. Still, in Paper II of this thesis, there were strong associations between the CPC on the one hand, and MMSE and NFL on the other hand. Although no study seems to have compared the CPC with detailed neuropsychological tests, these associations indicate that the CPC is related to the post-arrest brain injury. Our group has, in line with this, reported that serum NFL can differentiate between CPC categories [58]. As with the clinician-reported Glasgow Outcome Scale, the CPC and mRS are not designed to measure detailed cognitive function but rather to capture overall functional deficits [257]. Like we discussed in Paper II, the CPC and clinician-reports in general are concise but should not be the primary choice when aiming to measure detailed neurocognitive function.

Patient-reports

Other rating scales such as patient-reports and observer-reports are generally easy to administer and may also be more cost- and time-effective than performance-based tests [258]. Traditionally, there has been limited focus on patient-reports in resuscitation research [259]. Still, patient-centered care and patient and public involvement has recently gained importance with a pursuit to understand the impact of cardiac arrest from the unique perspective of the survivor [260]. No cardiac arrest-specific patient-reported outcome measure exists so generic measures such as the coarse TSQ are currently used, but promising efforts are underway. The weak association between the MMSE and TSQ in Paper II does put the finger on the drawback with patient-reports aiming to measure cognition. That the patient-reported measure appeared more

influenced by emotional problems is in accordance with other studies on ABI patients, that also have emphasized the effect of emotional aspects rather than cognitive impairment [157, 261, 262]. An understanding that these problems may be described as cognitive by the patients is desirable, so that the problems can be further investigated both cognitively and emotionally. Seldomly investigated systematically, reduced insight and self-awareness of the impairments in function following severe ABI may also influence the discrepancies between patient-reports and performance-based tests [263]. With that in mind, patient-reports are still relevant when evaluating general outcome and can be used to inform treatment recommendations paired with neuropsychological tests in the clinic [262].

Observer-reports

Observer-reports are useful complements to patient-reports, since observers who know the patient well can note relevant changes in their current daily life and may not be influenced by potential lack of insight following ABI [264]. In Paper I, the IQCODE-CA was not affected by the participant's premorbid cognitive function or education, which is an advantage of this approach. And yet, more anxiety and depression symptoms correlated with worse IQCODE-CA ratings. As exemplified with the original IQCODE, observer-reports can also be affected by mental health of the informant and the patient–informant relationship, and little is known about which informants supply the most accurate data [265]. The IQCODE-CA's associations with performance-based measures were lower than those of the original IQCODE, possibly due to different study populations. As discussed in Paper I, this currently insufficient convergent validity should be further investigated in other IQCODE-CA studies. Whilst there currently is a lack of other data focusing on observer-reports for the OHCA population, similar discrepancies between observer-reports and performance-based measures have been established among children with executive dysfunction, concluding that these perspectives cannot be used interchangeably [266]. Correspondingly, the IQCODE-CA should be used in addition to performance-based measures to improve the screening accuracy.

Implications for other areas important for neurocognitive outcome

Biomarkers

We used NFL as a proxy of hypoxic-ischemic brain injury in Paper II to explore its associations with the neurocognitive outcome methods, and not to evaluate the biomarker in its own right. Nevertheless, Paper II adds to the increased evidence of NFL as a versatile and very sensitive biomarker following OHCA. It is debatable if NFL can predict the long-term neurorehabilitation needs of each patient that survives OHCA, though, NFL may be utilized to explore associations with different neurocognitive outcome instruments. The construct validity of the instruments could be increased by helping us understand what the instruments measure; brain injury according to a sensitive biomarker such as NFL, or associated factors such as emotional problems and fatigue.

Affected brain structures

Paper IV did, consistent with our pre-specified analysis plan in Paper III, not include any measures of neuroimaging. The relationship between cognition and brain structure following OHCA has not been thoroughly investigated with imaging techniques. It has been speculated that this is because of many survivors having internal cardiac defibrillators which may not be safe for magnetic resonance imaging, or that they are considered as cardiac and not neurologic patients [267]. Still, based on earlier imaging studies [36, 267-270], the results from Paper IV indicate that brain regions associated with episodic memory such as hippocampus may have been affected among some OHCA survivors of this study. Hippocampus could be extra sensitive for the hypoxic-ischemic brain injury according to the selective vulnerability hypothesis [36]. Then again, most studies have reported a widespread pattern of brain damage in cortical and subcortical structures post-OHCA compared to MI controls and healthy controls [138, 267-271]. A recent mini-review indeed reported that diffuse cortical and deep grey matter lesions were the most common neuroimaging findings, suggesting that the domains of memory, executive functions, and processing speed all need to be assessed [272]. The lack of a pure amnestic syndrome was evident in Paper IV, since impairments in processing speed and executive functions were commonly observed as well, tentatively in line with this suggestion. This is however quite hypothetical.

Emotional problems have been hypothesized as a consequence of the neurological damage following OHCA, since brain regions associated with hypoxic-ischemic brain injury, anxiety and depression partly overlap [273]. Yet, to which extent the cognitive

functioning and emotional problems of the participants in Paper IV de facto corresponded with reduced volumes or cortical thickness cannot be answered.

Neurorehabilitation

Whilst post-discharge follow-up meetings according to guidelines are more common in regular care [54], cognitive and neuropsychological rehabilitation services are in parts of the world sparsely available for survivors of OHCA. This applies to industrialized countries as well. The fact that 29% of the OHCA survivors in Paper IV had a cognitive impairment according to our definition highlights that neurorehabilitation unarguably should be a possibility in the treatment planning. Mild cognitive impairment is common and often not easily recognized by health care professionals [189]. Survivors of OHCA without cognitive impairment could instead participate in standard cardiac rehabilitation [274]. All this emphasizes the necessity of a patient-centered approach. Formalized evaluations of neurorehabilitation programs or other interventions following OHCA are needed.

Strengths and limitations

Strengths

The papers included in this thesis were based on infrastructure from large and successful intervention trials. The papers of this thesis all included many participants, irrespective of their different approaches in the study design, which increases the statistical power of the results and enables sub-group analyses. Unlike many other similar works, in our most detailed study (Papers III and IV) we also used data from a matched non-arrest MI control group. This was made in an effort to separate the effects of the cardiovascular risk factor profile mostly shared by both cohorts, from cognitive impairment due to hypoxic-ischemic brain injury caused by the OHCA. The international multicenter infrastructure with ambitious main trial follow-ups also allowed us to explore relationships between different cognitive outcome methods and biomarkers, emotional problems, fatigue, insomnia, and cardiovascular risk factors. The outcome instruments were overall established both in clinical practice and OHCA research and generally had sound psychometric norms.

Limitations

The results of Papers I and II had a relatively low level of attrition but used cognitive instruments with lesser sensitivity than those of Papers III and IV. Alternately, Paper IV had higher levels of attrition (59% of eligible participants at the sub-study sites were included). This is probably partially because of the comprehensive approach of the TTM2 neuropsychological sub-study that required an examination separated from the main TTM2-trial follow-up. Selection bias, that those with excellent recovery may be more likely to say yes to being part of the study, cannot be ruled out. Since their study recruitment was not integrated into other study or health care follow-ups, the MI controls could instead have been more motivated to participate if they experienced subjective cognitive problems. Their overall performance without cognitive impairment indicate that this was not the case for a majority of the MI controls. All the same, the lower inclusion ratio has a negative impact on the generalizability of the results.

The OHCA survivors in Paper IV had lower rates of hypertension and diabetes compared to those of the MI control group. A lower proportion of OHCA survivors than MI controls also had STEMI as cause of initial cardiac event, which is associated with a higher risk of heart failure and concomitant cognitive impairment. Nevertheless, the generally adequate performance of the MI controls indicates that this did not have a greater influence on this cohort. Thus, the impact of these between-group differences on the background variables are unclear.

Most of the countries that participated in the TTM-trial (Papers I and II) and all countries that participated in the TTM2 neuropsychological sub-study (Papers III and IV) practiced WLST. Our results may only be translated to countries with similar intervention traditions as those of the papers in this thesis.

Many analyses were conducted, and the common problem of multiple comparisons cannot be ruled out (multiplicity; analyses involving multiple statistical tests entail a risk for erroneous inferences with false positive cases or "false discoveries"). Nonetheless, overall, our results are in line with earlier findings and appear valid from a clinical viewpoint.

We did not have information on the premorbid cognitive capacity of the participants when administering the performance-based tests. Some informant-reports such as the IQCODE-CA investigate cognitive change only and would therefore mitigate this problem. This is, however, dependent on accurate information from the informant. When the IQCODE-CA was administered (Papers I and II), we had no reliable method to estimate the accuracy of the provided information.

On the performance-based tests, we used a traditional test-based approach to measure cognition. This is associated with lower ecological validity and limited capacity to

reflect performance of everyday activities. We chose traditional neuropsychological and cognitive screening instruments since they focus on cognitive functions rather than activities and participation according to the ICF model. Most of our performance-based tests have neuroanatomical correlates and acceptable population norms. Instruments with an activity driven assessment approach could still be valuable resources in other settings.

No formal psychiatric evaluation beyond self-reports were used to confirm symptoms indicating emotional problems, fatigue, and insomnia. Especially emotional problems are known to have an impact on cognitive performance, so our inclusion of both cognitive and affective data made it possible to explore OHCA-associated relationships on this topic. Still, the relationship of cognitive function and emotional problems is an example of the chicken or the egg paradox. Causal links are hard to establish without controlling for psychiatric comorbidities or for premorbid cognitive capacity associated with familiar risk for major depressive disorder. This, as well as potential implications of the impairments and symptoms for the closest network of the OHCA survivors, has not been possible to investigate within the scope of the papers included in this thesis.

Conclusions

General conclusions

This thesis has established that cognitive impairment following OHCA is common in the late recovery phase. The findings of most importance in this thesis are summarized per paper below.

I. The informant-report IQCODE-CA had acceptable psychometric properties in an OHCA population and could be used alongside with performance-based measures when screening for cognitive impairment.

II. The clinician-report CPC was mostly related to hypoxic-ischemic brain injury according to NFL, but with a ceiling effect. Although associations between patient-reports and performance-based measures were weak, all four outcome methods correlated significantly with each other.

III & IV. Cognitive impairment on the neuropsychological tests was generally mild among OHCA survivors, but most pronounced in episodic memory, executive functions, and processing speed. OHCA survivors performed worse than MI controls. Diabetes and symptoms of anxiety, depression, and fatigue were associated with worse cognitive performance among the OHCA survivors.

In sum, the results of this thesis contribute with a practical and easy-to-use informant questionnaire to indicate post-arrest cognitive impairment, information on how the four neurocognitive outcome methods are related to each other and to hypoxic-ischemic brain injury, as well as the most comprehensive and detailed investigation of neuropsychological function after OHCA to date.

Clinical implications

Based on Papers I and II respectively, this thesis supplies initial evidence that the IQCODE-CA may be used, and that the four outcome methods may be combined, when assessing neurocognitive outcome post-OHCA. The between-methods

convergent validity of the four outcome methods was acceptable. This should however be further investigated with studies on predictive models.

Cognitive impairment following OHCA is common, which again was established in Paper IV. This strengthens the recommendation in guidelines that individuals who survive OHCA need follow-up even after successful CPR. This follow-up should utilize not only a cardiac perspective but a neurological/neurocognitive as well. It is imperative that all survivors undergo screening for cognitive difficulties relatively early post-arrest. Functional assessments and information on potential problems already before hospital discharge provide patients and caregivers with information on potential later challenges in recovery. The results from the studies presented in this thesis indicate that a shorter neurocognitive screening should consist of several outcome methods to increase the overall scope of the assessment. The instruments must be sensitive to indicate cognitive impairment. Based on the results from Paper IV, cognitive impairment is related to anxiety and depression symptoms as well as fatigue. These areas also need to be components of the routine screening. Only through a screening can mild and therefore relatively unseen difficulties be detected. This is a prerequisite for support and information to patients and their network, as well as a detailed neuropsychological assessment which can be used to guide team-based cognitive rehabilitation programs if necessary. At signs of impairment, the interventions could optimize the long-term recovery after OHCA and facilitate the return to as normal a life as possible for survivors and their relatives.

It should be noted that the current results mostly are presented on a large-scale level due to the quantitative nature of the studies. For clinical groups such as those included in this thesis, there are large individual variations and cognitive profiles. The variability in neuropsychological outcome in Paper IV highlights that tailored and holistic intervention approaches related to cognition should be used when needed. This certainly applies to surviving OHCA individuals, and, albeit to a lesser extent, MI individuals as well.

The results from Paper IV may be used to guide clinical neuropsychologists in their instrument selection during neuropsychological assessment of OHCA survivors. Similarly, these results could be useful when designing detailed test batteries in upcoming clinical studies on neurocognitive function following OHCA. There are other measures that already exhibit acceptable sensitivity but was not included in our test battery, such as the SDMT. That being said, the Brief Visuospatial Memory Test-Revised (BVMT-R), Rey Auditory Verbal Learning Test (RAVLT), and Trail Making Test (TMT) were all tests on which a large proportion of OHCA survivors performed worse than population norms.

Future perspectives

The accuracy of post-arrest screening models is a subject that warrants more research. At a relatively early stage after the OHCA, these models should identify possible cognitive impairment, emotional problems, and fatigue to provide adequate information and rehabilitation. It is unclear which predictive screening model that has the highest accuracy, feasibility, and is experienced as the most tolerable by the patients. The unique perspective of the patients should overall be further involved when researching cardiac arrest survivorship. The increasing number of networks for cardiac arrest survivors could be key collaborators to identify patient representatives.

The process of establishing evidence of validity is an ongoing, iterative process and not a one-off evaluation. More data on the utility of the IQCODE-CA, and preferably also a 16-items Short IQCODE-CA for improved feasibility, using confirmatory factor analysis is desirable to establish this as a psychometric sound questionnaire for informants of cardiac arrest survivors.

In that respect, future studies should continue the validation process of the MoCA as a cognitive screening measure following OHCA. This, along with important long-term data on neuropsychological function, will be further investigated in later works based on the results of the TTM2 neuropsychological sub-study.

The absence of a standard protocol for detailed testing of cognitive functioning with neuropsychological tests after OHCA has been discussed in several earlier studies. Establishment of routine outcome measurements would require broad acceptance from all stakeholders in a rigorous procedure. Built upon growing data on the sensitivity of individual instruments in prior research and expert panel opinions, recommendations on candidate measures could contribute with consistency for later neuropsychological OHCA studies. Findings from multiple studies with the same assessments could then be combined. Eventually, this may improve our understanding of different interventions to reduce the implications of the hypoxic-ischemic brain injury.

Future work should also provide more information on the relationship between OHCA-related brain injury, as measured by a sensitive biomarker such as NFL or by neuroimaging techniques, and neuropsychological tests of cognition following OHCA. This could help us understand the neuropathological and neuropsychological processes that occur with marked individual differences after a cardiac arrest. Cognitive impairment and emotional problems may be an effect of critical illness rather than an effect of OHCA. Therefore, a control group consisting of survivors of intensive care without OHCA could bring to light further perspectives on the neuropsychological effects of the intensive care environment.

Premorbid function, socioeconomic status, resilience, and cognitive reserve must be increasingly considered in neuropsychological OHCA-related research and clinical

practice. A similar and intricate field of research, which may gain importance in the future, is that of social and physical determinants of health in relation to emotional problems and cognition. Cognitive impairment may interplay with diverse factors such as cardiac anxiety, physical inactivity, cardiovascular risk or burden, and low ability to access social and health care. Awareness of which individuals that are at risk of these factors on a group level could in the long-term facilitate patient-centered rehabilitation programs which integrate cognitive and cardiac rehabilitation. Standardized evaluations of post-OHCA rehabilitation interventions, with at least a partial cognitive focus, are much needed.

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Neurocognitive function following out-of-hospital cardiac arrest

Cardiac arrest occurs when the heart suddenly stops beating. There is a risk of hypoxic-ischemic brain injury when the blood circulatory system cannot deliver oxygen to the brain, as an effect of the cardiac arrest. Those who survive a cardiac arrest can describe cognitive difficulties in everyday life, such as trouble remembering novel information or solving problems. This thesis explores the extent of neurocognitive impairment among survivors of out-of-hospital cardiac arrest. The thesis contributes with an informant questionnaire to indicate cognitive impairment, information on how four neurocognitive outcome methods are related to each other and to the brain injury, and the most comprehensive and detailed investigation of neuropsychological function after cardiac arrest to date.

ERIK BLENNOW NORDSTRÖM is a clinical psychologist at Skane University Hospital in Sweden, at present active within specialized neurorehabilitation services, and a member of Center for Cardiac Arrest at Lund University. He teaches in cognition and neuropsychology at the Lund University Psychology Program. This book is his doctoral thesis from the Department of Clinical Sciences Lund, Lund University.

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