Cognitive impairments after critical illness

Methodology, incidences and consequences

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Scientific environment

The Research Group on Intensive Care Outcome was formally created in 1999 by professor dr. med. Hans Flaatten and is situated in the Intensive Care Unit at Haukeland University Hospital and at the Department of Surgical Sciences, University of Bergen. The main focus is clinical research within the field of outcome in survivors after intensive care, but has also focused on quality assurance within intensive care.

Two dissertations have been produced from the group. In 2004 dr. med. Reidar Kvåle defended his thesis ”Long-term outcomes after intensive care” and dr. med. Atle Ulvik defended his ”Long-term outcomes after major trauma” in 2008. In 2011 cand. med. Kristian Strand at Stavanger University Hospital completed his PhD project on comparison of two different prognostic scoring models in ICU patients. Norwegian Registry of Intensive care (NIR) was established 1998, and has since 2004 been adopted and funded by Helse Vest (Governmental institution) as a National Quality Registry. The registry is lead by dr. med. Reidar Kvåle. Our ICU have for 10 years had a specially designed registry of adverse events. This registry now holds more than 3000 adverse events, and there is an ongoing research toward the epidemiology of such events in the ICU.

Our research group is internationally engaged in a study on the effect of an ICU diary on post traumatic stress disorder (PTSD) after intensive care. This project is a part of a European metacentre study, lead by the University of Liverpool. The so called RACHEL group consists of 8-10 ICUs in UK, Sweden, Norway, Italy and Portugal, and has previously collaborated in the field of outcome after ICU. The RACHEL group is led by Professor Richard Griffiths and Christina Jones (Research nurse) at the University of Liverpool. The main focus has been the development of PTSD in former ICU patients, and how to reduce this burden.

Contents

Abbreviations

AC	Arachnoid cyst
APACHE II	Acute physiology and chronic health evaluation II
ARDS	Acute respiratory distress syndrome
CA	Cardiac arrest
CAM-ICU	Confusion assessment method in the intensive care unit
CANTAB	Cambridge Neuropsychological Test Automated Battery
CCI	Charlson co-morbidity index
DMS	Delayed matching to sample
GCS	Glasgow coma scale
HRB	Halstead Reitan battery
HRQOL	Health related quality of life
ICU	Intensive care unit
IED	Intra/extra dimensional shift
MMSE	Mini-mental state examination
MOT	Motor screening test
NIR	Norwegian Intensive Care Registry
OHCA	Out-of-hospital cardiac arrest
PAL	Paired associate learning
POCD	Postoperative cognitive decline

PTSD	Post traumatic stress disorder
SAPS II	Simplified acute physiology score
SF-36	Short Form 36
SOC	Stockings of Cambridge
SOFA	Sequential organ failure assessment
TH	Therapeutic hypothermia
WMS-R	Wechsler memory scale - revised

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Bergen, November 2011 Johan Torgersen

Introduction

"But if life itself is good and pleasant (...) and if one who sees is conscious that he sees, one who hears that he hears, one who walks that he walks and similarly for all the other human activities there is a faculty that is conscious of their exercise, so that whenever we perceive, we are conscious that we perceive, and whenever we think, we are conscious that we think, and to be conscious that we are perceiving or thinking is to be conscious that we exist..."

Aristotle (382-322 BC) – Nicomachean Ethics

Cognitive function is a term used by the psychological and sociological sciences to describe abilities emphasized by Aristotle as necessary for human existence: Perception and thinking. Research has revealed the complex role of cognitive functions in human mental processing. Examples of cognitive functions are short-time memory, forced decision-making, spatial memory, executive functions, reaction time, motor speed and verbal memory. All these functions are involved in one or more of the key aspects of cognition: perception, storage, recalling or processing and further to use the acquired knowledge.

Various diseases may affect cognitive functions [1, 2]. At the same time intact cognitive functioning is an asset for patients both during illness and rehabilitation. During critical illness most patients will experience altered level of cognitive performance. This thesis focuses on the effect of critical illness on cognitive functions in former intensive care unit patients.

Abstract

Background

Brain dysfunction describes the wide range of alterations in brain function from persistent vegetative state to minor cognitive impairments. It has become evident that brain dysfunctions that arise during an intensive care unit (ICU) stay are associated with mortality, morbidity, post-ICU functional status and rehabilitation. Brain dysfunction in ICU patients is therefore of major interest both in clinical practice and research.

Cognitive impairment is one of several types of brain dysfunctions that may become evident after critical illness. The aims of this thesis were to document the incidences of cognitive dysfunction after critical illness, to investigate the post-ICU development and effects of cognitive functions and, if possible, to point out etiological and predisposing factors for such impairment.

To achieve this, we needed a neuropsychological approach to our patients. We chose to use the Cambridge Neuropsychological Test Automated Battery (CANTAB) as our method for evaluating cognitive function. CANTAB is a semi-automated neuropsychological test battery applied on a laptop PC. The program contains integrated normal reference population scores, which facilitate description of the tested patients' level of cognitive function and the statistical handling of the results. CANTAB can be administered in an every day setting by non-specialised personnel.

Main objectives:

1: To investigate causes and consequences of cognitive impairment in patients who have survived critical illness.

2: To establish and validate CANTAB for assessing cognitive functions in Norwegian hospitalised patients

Patients and methods

In order to establish and validate CANTAB we performed two validation studies in two Norwegian patient cohorts. Arachnoid cysts (ACs) are known to cause cognitive dysfunction because they compress neighbouring brain tissue; it has also been documented that decompression of the cyst improves cognitive functions. We investigated if CANTAB could detect the same cognitive improvements after decompression of temporal lobe cysts. Reproducing such cognitive improvements would establish construct validity of CANTAB. In order to establish criterion validity for CANTAB we tested a group of patients with epilepsy who were also tested neuropsychologically with a traditional battery, the "gold standard". In the AC study CANTAB was run in parallel mode meaning that we could only compare results from before and after testing. Comparison to the integrated reference population can only be done with CANTAB in clinical mode as applied on the epilepsy group. Because of this we could establish if the epilepsy patients were more cognitively impaired than the reference population. This was not possible with the AC patients.

To evaluate the effect of being critically ill on cognitive function we completed two studies on patients who had survived critical illness. Both studies included only patients with no pre-ICU increased risk of cognitive dysfunction and who had not suffered from primary or secondary cerebral damage before or during ICU stay.

The first study was on patients who had survived out of hospital cardiac arrest (OHCA) with a good functional outcome and who had been treated with therapeutic hypothermia. These patients were assessed more than one year after the cardiac arrest with CANTAB, Short Form 36 (SF-36) for assessment of health related quality of life (HRQOL) and cerebral performance category (CPC) for assessment of functional level.

In the second study we investigated a non-selected group of ICU survivors. Patients showing no delirium and with a Mini mental state examination (MMSE) score ≥ 24 at ICU discharge were tested with CANTAB immediately and then again after three and twelve months. We also gathered information on survival, institutionalisation after

hospital discharge, severity of disease, co-morbidity, length of ICU stay and days on ventilator support to look for risk factors of cognitive function and possible consequences of such impairment.

Results

Previous studies have shown that ACs have a predilection for the temporal fossa and that they may interfere in a reversible manner with temporal lobe function; thus the dyscognition is normalised after a surgical cyst decompression. When testing AC patients with a CANTAB battery, we found significant cognitive improvement after decompression of the AC in tests that are designed to test for temporal lobe functions. However, we found no postoperative improvement in tests that were designed to probe frontal lobe functions. These observations establish construct validity of CANTAB.

In the group of patients with epilepsy we found that traditional testing and CANTAB testing resulted in the same classification into patients with or without cognitive impairment in 12 of 15 patients. Thus, there was an 80% agreement within the two tests. In addition several previously documented and clinically logical significant correlations were documented when correlating results from the two tests. This establishes criterion validity of CANTAB.

We tested a group of 25 patients who had survived for more than one year after cardiac arrest with a good functional outcome (i.e. CPC 1 and 2). The group did not differ from a Norwegian reference population in HRQOL. However, 52 % of the patients were nevertheless classified with a cognitive dysfunction.

We included 55 patients in our study on former general ICU patients. Immediately after ICU discharge 64% of classifiable patients had cognitive impairments. This figure dropped however to 11% and 10% after three and twelve months, respectively. We found no associations between pre- or in-ICU factors and the development of such impairments. There were no associations between cognitive impairments at

discharge from ICU and outcome factors such as mortality, institutionalisation or HRQOL.

Conclusions

We have for the first time established construct validity and criterion validity of CANTAB in Norwegian patients.

Cognitive impairments are common after cardiac arrest and critical illness. It seems that cardiac arrest patients are in higher risk of developing permanent cognitive impairments than general ICU patients. We found no associations between ICU-related cognitive impairments and possible aetiological factors, morbidity, mortality or health related quality of life.

List of publications

Torgersen J, Strand K, Bjelland TW, Klepstad P, Søreide E, Wentzel-Larsen T, Kvåle R, Flaatten H. Cognitive dysfunction and health related quality of life after cardiac arrest and therapeutic hypothermia. Acta Anaesthesiologica Scandinavia 2010; 54: 721–728

Torgersen J, Helland CA, Flaatten H, Wester K. Reversible dyscognition in patients with unilateral, middle fossa arachnoid cyst revealed by a laptop based neuropsychological test battery (CANTAB). Journal of Neurology 2010; 257: 1909-1916

Torgersen J, Engelsen B, Flaatten H, Gramstad A. Clinical validation of Cambridge Neuropsychological Test Automated Battery in a Norwegian epilepsy population. Submitted Journal of Behavioural and Brain Science 2011.

Torgersen J, Hole JF, Kvåle R, Wentzel-Larsen T, Flaatten H. Cognitive impairments after critical illness. Acta Anaesthesiologica Scandinavia 2011; 55: 1044–1051

1. Background

1.1 Cognition and disease

1.1.1 Cognition

Cognition is a term used since the early 1500's to describe acquired knowledge. Its origin is the Latin verb *cognoscere* meaning *"to get acquainted with"* or *"to get to know"*. Even though cognition is a word not frequently used in modern English, we find the same origin in words like *recognition* meaning both *"to get to know again"* or *"acknowledge"* and *cognizance* meaning "*knowledge"* or "*awareness"*. Not surprisingly, in science cognition is often described as the *"knowledge of knowing"*. After World War II the term was adopted by the psychological and sociological sciences and gained its role as a clinical and scientific term as the modern cognitive psychology emerged. A modern textbook of cognition elaborates and defines cognition as: "The acquisition, storage, transformation and use of knowledge" [3].

The key issue for sciences focusing on cognition and cognitive functions is the acquiring of knowledge and aspects of knowledge processing: our ability to perceive the world through our senses, our capacity to store information, how we recall information, how we process the information both during storage and recollection and not at least: how we use the acquired and stored knowledge. After input is delivered through our senses the brain conducts all further processing. Numerous functions involved both in perception, storage, recalling, transformation, and executing have been described and partly located in the brain, but the true nature of cognitive functions is not fully revealed. When knowledge is used during tasks of different difficulty levels, cognitive functions may display a wide range in performance in the same human or between humans. Both brushing our teeth in the morning, driving a car, completing a game of chess or intubating a patient demands intact cognitive functions directed exactly towards the skill at test.

1.1.2 Cognitive psychology

Cognitive psychology denotes a process-focused approached to psychology. In this theoretical orientation a person's knowledge and the connected mental processes are emphasised and used to describe behaviour, skills and function. Cognitive psychology can therefore be distinguished from other psychological orientations such as behaviourism or the psychodynamic approach. In behaviourism observable behaviour is the central aspect. The psychodynamic approach focuses on our unconscious emotions when describing behaviour, skills, function and changes in these. In contrast, cognitive psychology explores concrete processes such as memory, attention, planning, or executive function to describe the same phenomena [3].

Cognitive psychology leans on several different scientific directions and traditions: Philosophy, neuropsychology, neuroscience, artificial intelligence and even more. In neuropsychology the focus is on the evaluation of both emotional or psychosocial problems and the assessment of cognitive function, where the latter is the core issue. The neurosciences focus more on the *structures* associated with mental processes and their *location*. Examples of such fields of interest are fMRI and neurophysiology that can describe areas of the brain involved and neural pathways used when the human brain is active. The neuropsychologist evaluates to a larger degree the *function and use* of these structures or pathways during mental processing rather than the structures themselves.

When approaching cognitive functions, the neuropsychologist can choose from a wide selection of validated cognitive tests aimed at specific functions. Cognitive tests are traditionally administered as pen/paper tests, systematic interviews or by solving tasks under observation. The composition of test-batteries, i.e. several tests administered together to explore several functions or the same function from different views, has proven to be of great advantage. This makes it possible to evaluate intra-test variability, level of performance and how possible defects appear, thus indicating type of brain affection. Further interpretation of these results can give the clinician or researcher information about the patient's cognitive functions and dysfunction [4].

These test batteries are in general not validated as a unit; this constitutes a methodological problem. On the other hand, single tests are often validated and in particular construct validity is established [4]. When establishing construct validity, patients with lesions or diseases known to affect particular parts of the brain are examined; the resulting deficit can then be assigned to that area of the brain.

1.1.3 Cognition in disease

It is well documented that many diseases and conditions may affect cognitive functions. All patients with primary brain diseases (e.g. brain injury, epilepsy, apoplexy) carry the risk of developing cognitive dysfunction at some stage of the disease [4-6]. In addition patients with extra-cerebral conditions such as renal failure, liver failure or cardiovascular disease also show increased risk of developing cognitive dysfunctions, even without any known brain injury [2]. This indicates several etiologic causes of cognitive impairment in patients. Primary brain disease may cause brain cell dysfunction and death and hence altered cognitive function. Other, extra-cerebral diseases may cause reduced brain function for numerous reasons. Chronic obstructive pulmonary disease [1] or adult respiratory distress syndrome [7] may cause hypoxia, either acute or chronic, which affect brain cell function or cause cell death. In other diseases, such as cardiovascular disease, altered cerebral perfusion may have the same effects. In patients with renal failure the cognitive deterioration may be caused by increased level of circulating metabolites or toxins with negative effects on brain cells. The investigation of cognitive function in different groups of patients has led us to believe that the development of cognitive dysfunction during disease is multifactorial and may be explained by different mechanisms.

Not only are the causes of cognitive dysfunction diverse, so is also the form with which the cognitive affection present itself. In cerebral conditions like persistent vegetative state, minimally conscious state, delirium or dementia, the patients' ability to acquire, store, transform, or use knowledge is grossly altered, and such patients are

markedly cognitively impaired. Patients with no cerebral blood flow above the foramen magnum have lost all cognitive function permanently and are considered to be dead. When considering patients with severe cerebral damage, the Guidance for end of life treatment from Norwegian Health Authorities in fact recommend that decisions regarding continuation of treatment or ending treatment can be based on the patients expected possibility to acknowledge one-self or be aware of or respond to the surroundings [8] . If there is no hope for such awareness, further treatment is regarded meaningless. Evaluation of cognitive function is therefore relevant within the full range of cerebral functioning and in patients with any kind of cerebral affection.

1.1.4 Critical illness

Critical illness is defined as a disease or injury with threatening or manifest failure of one or more vital organ functions. Intensive care is not only directed towards causal diagnosis and treatment, but also the evaluation of organ function and, if necessary, organ function support. The main organ systems in intensive care are the respiratory system, the circulatory system, the central nervous system (CNS), the kidneys, blood homeostasis, and the gastrointestinal tract. The most common primary causes for admittance to an intensive care unit (ICU) are respiratory failure, cardiovascular failure and severe disease in the CNS [9]. Some of the diseases can strike previous fit persons and others primarily affect patients with an underlying disease or organ affection. The risk of developing organ dysfunction increases if the organ already suffers from disease or is weakened for other reasons. This also applies for disease in the CNS.

The systemic impact of serious disease or trauma may trigger reactions in other organs than the ones primary affected. Systemic inflammatory response syndrome (SIRS) denotes a condition of vast immunologic activity often triggered by disease such as serious infection or major trauma. The inflammatory response may affect potentially all organs with a resulting multi-organ dysfunction or failure. All ICU patients may therefore ultimately develop multi-organ failure during critical illness.

The aetiology of both primary and secondary organ failure is diverse and complex. Organ failure may be caused by or cause cellular hypoxia. Patients with respiratory failure may transitionally suffer from hypoxemia with resulting cellular hypoxia in vulnerable organs. This is an example of primary organ dysfunction (respiratory) with secondary dysfunction in other organ systems. Altered cellular activity may eventually cause organ dysfunction with clinical relevance. Renal failure is often caused by such hypoxic events. On the other hand, disease in the cardiovascular system can cause tissue hypo-perfusion with resulting cellular hypoxia even without simultaneous hypoxemia. The reduced detoxification in dysfunctional kidneys may cause negative effects on cells in other organs and hence contribute to multiple-organ dysfunction.

1.2 General perspectives on the scientific approach to cognitive impairments in ICU patients

1.2.1 Pre-ICU level of cognitive function

When evaluating cognitive functions in ICU survivors one main challenge arises: we often lack knowledge of the patients pre-ICU level of cognitive function. Through a thorough anamnesis it is possible to discover severe dysfunction like dementia or patients with increased risk of cognitive dysfunctions due to pre-ICU factors, such as former stroke or drug/alcohol abuse. When the focus is set on the effects of being critically ill, it is possible to exclude such patients aiming for a cohort with presumptive cognitively intact individuals. But even so, the normal variation in level of cognitive function is wide and in addition a portion of the general population will have pre-existing, but not clinically acknowledged dysfunctions. Given the non-elective nature of most ICU admittances, it is difficult to evaluate the ICU survivors' pre-ICU level of cognitive performance in a way that is directly comparable with the results from after-ICU cognitive testing. Regarding the effect of surgery and/or general anaesthesia on cognition, it is possible to perform a prospective study, measuring the cognitive level before and after surgery to see if there is a

postoperative cognitive decline (POCD). As the pre-ICU cognition level is often not known, a similar approach is difficult in ICU survivors. Instead of measuring cognitive decline, we are confined to classifying the patients as being with or without cognitive impairments or comparing them with reference groups [10].

1.2.2 Description of cognitive level of performance

The description of cognitive performance after critical illness must rely on either comparison with a normal population, a control group or repeated measures in a disease specific group. Cognitive functions are regarded as being normally distributed in the general population. This enables us to express the former ICU patients' level of cognitive performance relative to the general population or other patients. Neuropsychological test batteries are often supplied with such normal reference populations making it possible to express the tested patient's level of cognitive performance as an index or even z-scores.

Z-scores are normalised scores based on the comparison of the patients result with the results in a reference population. The z-score equals how many standard deviations the results from the patients deviate from the mean score in the reference population. A result equal to the mean in the reference population will give a z-score of 0 while poorer results will have a negative z-score and better results will have a positive z-score. Z-scores can be used in classification systems to sort patients into groups of impaired or not impaired patients. In a paper by Jackson et al. the authors outline several aspects of evaluation of cognitive impairments in ICU survivors [10]. They propose the following criteria for categorising a patient with a cognitive impairment: At least two out of ten z-scores from neuropsychological testing below -2.0 or at least three out of the same ten z-scores below -1.5. This is regarded as rather strict criteria for categorising a patient with a cognitive impairment.

The level of cognitive performance in a test group can be described either by making comparison with a normal population or by establishing control groups. When

establishing a control group, it is possible to match it to the ICU group. Then it is possible to control for several other factors than the ICU survival that may have affected cognitive function.

It is also possible to repeat cognitive testing of a patient over a defined time-period. This allows us to investigate the development of cognitive impairment in a time perspective. It is possible to categorise patients at each point of time and also to make both one-sample group comparison and independent sample group comparison. This enables us to establish whether one group of patients has a slower recovery or whether specific groups sustain a high incidence of cognitive impairments.

Given the wide range in level of cerebral performance patients can display after critical illness, several tools are often needed to describe all patients in one group. Sensitivity and specificity of each tool will vary according to the tested patient's level of performance. MMSE is suitable to address patients with severe cognitive impairments while more complex neuropsychological test batteries must be applied if subtle changes are to be revealed.

2. Study objectives

This thesis has two main objectives:

1: Investigate cognitive impairments and their causes and consequences in non-delirious patients with MMSE ≥ 24 who have survived a period of critical illness

2: Establish and validate CANTAB for assessing cognitive functions in Norwegian hospitalised patients

To approach the main objectives mentioned above, several aims have been formulated:

1 A: Estimate the incidence of cognitive impairments in a group of ICU survivors immediately after ICU discharge

1 B: Follow the development of cognitive impairments over the first year after ICU discharge

1 C: Estimate the incidence of cognitive impairments in survivors of out-of-hospital cardiac arrest (OHCA) with high functional outcome one year or more after the arrest

1 D: Investigate whether being critically ill affects cognitive function

1 E: Describe the characteristics of cognitive impairments after critical illness

1 F: Describe possible pre-ICU or in-ICU predictors of cognitive impairments

1 G: Investigate the effect of cognitive impairments on mortality, morbidity and health related quality of life after ICU discharge

2 A: Establish and evaluate the practical use of CANTAB in an ICU setting and post-ICU setting

2 B: Establish construct validity of CANTAB in a Norwegian hospitalised population

2 C: Establish cross-test validity of CANTAB in a Norwegian hospitalised population

2 D: Establish valid criteria for classification of cognitive impairment in former ICU patients based on results from CANTAB

3. Patients and methods

3.1 Patients

We recruited patients from three hospitals: Haukeland University Hospital (HUH), Stavanger University Hospital (SUH) and St. Olav University Hospital (SOUS) in Trondheim. HUH is a 1000-bed tertiary referral hospital for about 1 000 000 inhabitants in Western Norway. The intensive care unit at HUH is a 10-bed predominantly surgical (70 %) ICU. Critically ill neonates, burn patients and uncomplicated post operative patients after cardiac surgery are treated in separate ICUs. In 2009 470 patients were treated in this ICU. All common ICU procedures, except ECMO, are performed. All patients in the study on cognitive impairments after critical illness were recruited from this ICU.

From Department of Neurosurgery at HUH we recruited patients for the study on ACs. This 27-bed department is a tertiary referral centre for all neurosurgical patients in Western Norway and offers all common neurosurgical procedures. In addition, the department serves the majority of Norwegian patients with a vestibular schwannoma, and all Norwegian patients treated with gamma knife. Some patients with ACs from abroad are also referred to the neurosurgical department at HUH for advice or second opinion, or even treatment.

All patients included in the study on epilepsy patients were recruited from Department of neurology at HUH. The department serves both as a local hospital for about 350 000 patients and as a tertiary referral centre for Western Norway.

All patients included in the study on cognition after OHCA were recruited from ICUs at the SUH and the SOUS. The SOUS is a tertiary referral centre with a regional catchment population of approximately 660 000. The CA patients are recruited from both a 10-bed mixed-ICU and an eight-bed coronary care unit. A total of 1303 patients were treated in these ICUs in 2008.

At SUH all ICU patients needing respiratory support are treated in the same mixed medical/surgical ICU including CA patients. This ICU is the only ICU in the hospital and has approximately 800 admissions per year. There are 12 beds in the ICU, but normal staffing only allows for the use of 7 beds when a nurse patient ratio of 1:1 is to be ensured. The ICU at SUH provides intensive care for approximately 320 000 inhabitants in the southern part of the county of Rogaland.

3.2 Classification of cognitive impairments

Confusion assessment method in the ICU (CAM-ICU) and Mini-mental state examination (MMSE) are both used to diagnose brain dysfunction in ICU patients. We used these tools to exclude patients with delirium and MMSE score <24 from our studies. Patients with MMSE ≥ 24 were further assessed with CANTAB and were classified into having a cognitive impairment or not. A cognitive impairment was diagnosed according to Jackson's criteria after CANTAB assessment. The results reported from CANTAB that were used to classify patients are presented in table 6. Jackson's criteria are described in section 1.2.2.

3.3 Cambridge neuropsychological test automated battery (CANTAB)

3.3.1 General introduction

By establishing neuropsychological testing we aimed to make neuropsychology a part of the scientific and the clinical evaluation of former critically ill patients. When assessing cognitive functions in survivors of critical illness, we wanted to apply a neuropsychological test that could be administered by the ICU personnel. The test battery had to provide us with tests that evaluate cognitive domains often affected after critical illness; it should be possible to administer in an ICU setting or in the ward and it should produce standardised scores that can be related to a reference population. Furthermore, the test battery should be able to provide robust information even when available test duration was limited due to the condition of the patients.

The range in difficulty level within each test had to be wide ensuring that most patients could solve some tasks and few patients could solve all (floor/ceiling effects). Traditional neuropsychological testing is usually administered by a specialist in neuropsychology, which makes such tests resource demanding. These batteries are often complex and time consuming, which make them unsuitable for many of the critically ill patients or for those who just has emerged from their critical phase.

CANTAB is a semi-automated laptop based cognitive test apparatus containing 22 different cognitive tests. This enables doctors and nurses in the ICU to administer the test after a short instruction prior to using. The tests assess cognitive functions within the main cognitive domains: Visual memory, semantic/verbal memory, executive function, attention and decision making/response control. The automated tests are based on traditional cognitive tests developed at the University of Cambridge. With CANTAB is possible to compose different test batteries based on the 22 tests available to explore the clinical or scientific issue in focus. All tests are non-verbal, consisting of geometric designs or simple shapes and language proficiency is necessary only to understand the verbal instructions prior to task initiation. Range in difficulty level within each test is wide, thereby reducing both floor and ceiling effects. It is also possible to create relevant test batteries, which can be administered during 10-15 minutes, thus enabling us to approach exhausted ICU patients as well.

The tests or test batteries are applied on a laptop with a touch sensitive screen. The patient is presented for the different tests on the screen and responds by pressing the screen (picture 1). Both presentation of the tests and the registration of the patient's response on each test are done automatically. This is one of the main advantages of such automised testing: inter-tester variability is low. Further the automatic registration of results allows for immediate processing and storage in the integrated soft-ware. CANTAB contains an integrated English reference population allowing for immediate comparison with a group of age and sex matched controls. Cognitive functions are regarded normally distributed in the population. Thus each patient's result on each test can be expressed as a z-score by comparing the patient's raw score with the mean raw score in the reference population. This simplifies statistical

analysis of the results and categorisation of patients based on recommended criteria for such classification.

CANTAB can be run in to modes: clinical mode or parallel mode. The main feature of clinical mode is the comparison of the patient's results with the reference population allowing investigation of the level of cognitive performance for each tested patient. In the parallel mode, the main advantage is that the same CANTAB test can be run repeatedly, but the content in each test will change, thereby one might hope to eliminate or reduce learning effects in the test situation. This mode is eligible to follow-up patients where development over a period of time is desirable. In the parallel mode comparison with the reference population is not possible.

Picture 1: CANTAB applied on an ICU patient. This patient is dependent on respiratory support through a tracheostomy. The test is done bedside and accompanied only by the laptop and the investigator

Some issues arise that have to be addressed before applying CANTAB and interpreting the results. Neither CANTAB tests nor the use of its reference population has been validated in Norwegian patients. Even though cultural independence is

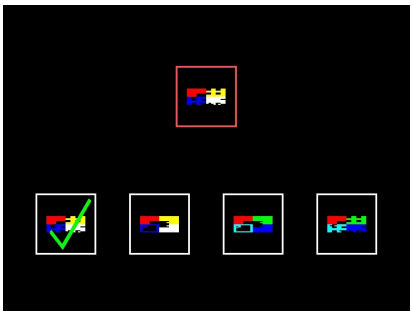
claimed [11] and it is rather unlikely that there are large differences between the Norwegian and English normal population, validity had to be established for CANTAB also in Norwegian populations. Comparisons with traditional tests are sparse, which makes it debatable how CANTAB tests can replace traditional tests. CANTAB batteries are suitable for cognitive screening and for research issues, but regarding more thorough clinical diagnosing CANTAB has not yet proved its equality to traditional testing. Below the tests are described in the order they appear during a test session.

3.3.2 Motor Screening test (MOT)

Picture 2: Motor screening test. The patient is instructed to press ten flashing crosses, appearing one by one, as soon as they appear on the screen.

MOT is an introduction test recommended to use when starting the CANTAB test battery. Patients who do not comply with this test are not regarded suitable for further CANTAB testing. From MOT it is possible to report speed of response and accuracy of pointing. We chose to report speed of response from MOT.

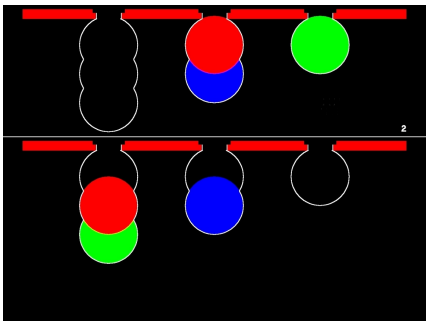
3.3.3 Delayed matching to sample (DMS)



Picture 3: Delayed matching to sample. The patient is presented with one of 30 possible non-figurative patterns on the upper half of the screen. Subsequently the patients then should pick the previously presented pattern from four similar patterns appearing on the lower half of the screen. The four patterns appear either simultaneously or after delays of zero, four or twelve seconds.

DMS is a test for memory and forced decision-making. DMS tests both immediate and delayed recognition memory. By comparing results on easy tasks (0 seconds) with results from difficult tasks (12 seconds delay) it is possible to differentiate between the abilities to store information and recall information. DMS may be sensitive to damages mainly in the medial temporal lobe, but is also dependent on some inputs from the frontal lobe [12]. The most reliable result to report from this test was “total correct” answers, but we chose to report results on both “latency” and the number of correct responses on 0 and 12 seconds. Thereby we hoped to be able to distinguish between impairments in storing and recalling and also to differentiate between immediate and delayed memory.

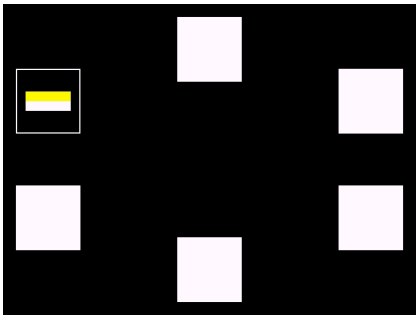
3.3.4 Stockings of Cambridge (SOC)



Picture 4: Stockings of Cambridge. The patient has to rearrange the three coloured balls displayed in the lower half of the screen to match the pattern in the upper half. The difficulty level increases as the minimum moves needed for rearranging the balls increases from two to five.

Stockings of Cambridge is regarded a test of executive function and requires spatial abilities and strategic planning. The abilities tested by SOC is claimed to give a measure of frontal lobe function [13]. As with DMS, is it possible to compare tasks with different difficulty level. We chose to report the number of "problems solved in minimum moves", as this has been shown to be the most reliable result [14, 15]. In addition, we reported the "mean number of moves" and "subsequent thinking time" on 2 and 5 moves. Thinking time was only reported in the arachnoid cyst study.

3.3.5 Paired associate learning (PAL)



Picture 5: Paired associate learning. One by one the white boxes "open" and reveals an empty space or a pattern. The patient has to remember the location of these patterns and then point out where on the screen the pattern initially was shown. The difficulty level increases as the number of boxes filled with patterns increases.

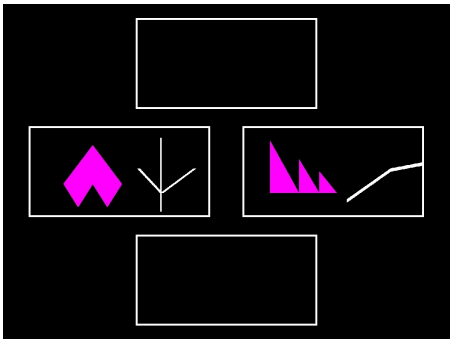
Paired associate learning is a test for episodic and visual memory but also depends on the ability of spatial planning. The performance in PAL depends mainly on inputs from the temporal lobe, but also from the frontal lobe [16]. We chose to report "total errors" and "total trials" needed to complete the tasks indicative of level of impairment. In addition "first trial memory score" was reported enabling us to report results from patients who did not complete the test because of high difficulty level in the last task. All reported results show high test-retest correlations.

3.3.6 Big/little Circle (BLC)

Picture 6: Big/little circle. The big and the little circle appear at changing locations on the screen. The patient is instructed to point on the little circle for the first 20 appearances and then on the big circle for the following 20.

This test is a simple preparation test that is recommended to precede the intra/extra dimensional shift test to prepare the patient for this complex task. No results reported.

3.3.7 Intra-extra dimensional set shift (IED)



Picture 7: Intra-extra dimensional set shift. Four boxes are shown on the screen. In two of the boxes there are one or two patterns. One of the patterns is the correct one to point at. The patients are supposed to disclose which one by a try-and-fail method. When the correct pattern is pointed at, the feedback "correct" is given. Then the patients should keep on pointing at the correct pattern until the rules are changed and another pattern is the correct one to point at. The rule changes after the patient has pointed at the correct pattern 9 times and by doing this verifies that the rule is disclosed. After the rule changes, the patient has to discover the new rule by finding the next correct pattern to point at repeatedly. Nine rules have to be disclosed to complete the whole test.

IED is considered a test of executive function and depends primarily on fronto-striatal regions of the brain. IED tests visual discrimination and attentional set formation. It also tests maintenance, shifting and flexibility of attention [17]. "Number of tasks solved" was the most reliable result to report. In addition to this we reported "total errors" and "total trials" enabling us to differentiate between patients with poor achievements, i.e. those who solved few tasks. The BLC and IED tests were only used in the AC study to add an extra control test for frontal function.

3.4 Overview: additional diagnostic tools, registers and scoring systems

3.4.1 Cerebral performance category (CPC)

Cerebral performance category is a scoring system that is used to categorise the functional outcome after cerebral damage. It is frequently used to assess functional outcome, also in cardiac arrest survivors [20]. CPC confines both consciousness and other neurological disorders connected to the CA. Criteria for scoring are shown in table 2. CPC 1 and 2 are considered good functional outcome.

Table 2: CPC score and function level

CPC score	Function level
1	Good cerebral performance
2	Moderate cerebral performance
3	Severe cerebral disability
4	Coma or vegetative state
5	Brain death

3.4.2 Mini-mental state examination (MMSE)

The Mini-mental state examination is an established and validated screening tool for cognitive impairments in general [21]. This test evaluates cognitive function through the evaluation of orientation, memory, counting, language and copying skills. The score range is 0-30 and patients with MMSE <24 are considered cognitively impaired. MMSE does not differentiate between cognitive domains and does not address more subtle cognitive changes.

3.4.3 Short Form 36 (SF-36)

Short Form 36 is a general measure tool for assessing health related quality of life and measures eight dimensions: physical functioning, role physical, role emotional, social functioning, bodily pain, vitality, mental health and general health. The SF-36 has been validated in a Norwegian population [22]. Results from SF-36 can be compared with age and sex matched reference populations allowing us to describe the tested patients' HRQOL. SF-36 has been frequently used in research on survivors of critical illness and also in our department. It has previously been documented that HRQOL measured with SF-36 is significantly reduced after critical illness and also improves during the two first years after discharge from ICU [23, 24].

3.4.4 Charlson co-morbidity index (CCI)

Charlson Co-morbidity index (CCI) was used to document co-morbidity and to study the effect on possible brain dysfunction during ICU stay. CCI assesses diseases such as hypertension, COPD, diabetes, HIV, autoimmune disease, renal failure, and others to describe co-morbidity. CCI gives an age-adjusted score based on the patient's pre-existing medical conditions and can be used to estimate the risk of death based on co-morbid disease in longitudinal studies [25].

3.4.5 Sequential organ failure assessment (SOFA)

The SOFA score system describes organ dysfunction and failure in the critically ill. It can be used to assess the effects of therapy on the course of organ dysfunction or failure. The SOFA scoring is based on objective assessment of function in six organ systems: Respiratory, coagulation, liver, cardiovascular, central nervous system and renal function. Dysfunction is classified from 0 (normal) to 4 (most abnormal) hence giving a score range from 0-24 [26]. In our department SOFA score is assessed every morning. We chose to report maximum SOFA score as an indication of severity of illness taken the whole ICU stay into consideration.

3.4.6 Simplified acute physiology score II (SAPS II)

SAPS II collects information on 17 variables documented to affect hospital mortality in critically ill patients. Twelve of the variables are physiologic and describe organ affection during the 24 first hours after admission to the ICU. Further age, type of admission (scheduled surgical, unscheduled surgical or medical) and the presence of three possible underlying medical disorders (AIDS, metastatic malignancy, or haematological malignancy) are registered [27]. Based on these variables, hospital mortality is predicted. SAPS II can also be used as an expression of severity of illness at admission to the ICU.

3.4.7 Registry of intensive care activity (REGINA)

REGINA is a local registry collecting information about the individual patient regarding the stay in our ICU at HUH. In REGINA information such as age, sex, CCI, SOFA score, max SOFA score, SAPS II, SAPS III, length of stay, days on respiratory support and hospitality mortality is gathered. This was our main source of such information for each patient. If REGINA could not supply us with this information, journals or the electronic ICU chart (ICIP) were reviewed.

4. Summary of papers

Paper 1: Reversible dyscognition in patients with a unilateral, middle fossa arachnoid cyst revealed by using a laptop based neuropsychological test battery (CANTAB)

Arachnoid cysts (AC) are benign, congenital, space occupying malformations of the arachnoid. It is previously documented that ACs affect cognitive functions influenced by underlying areas of the brain and that this dysfunction can resolve after surgical decompression of the cyst. CANTAB has not been validated in Norwegian populations before. In this study we wanted to explore whether CANTAB could reveal the specific cognitive improvement after surgical decompression that one could expect according to cyst's location, and thus to validate the test battery's neuro-anatomical specificity. We applied CANTAB in the parallel mode thus not enabling us to classify the preoperative level of cognitive function compared to the reference population. We prospectively tested patients with ACs in the temporal region with two memory tests that depend on inputs from a normal functioning temporal lobe and two executive tests more sensitive to frontal lobe function. Secondary we wanted to investigate HRQOL and possible changes in HRQOL after surgery in these patients. Twenty-two adult patients with unilateral temporal lobe AC were included and went through clinical examination, neuro-imaging, CANTAB, and they filled in SF-36 for evaluation of HRQOL. After a minimum of three months the patients where scheduled for a postoperative control. Fifteen patients were followed-up according to protocol including CANTAB. These 15 patients showed significant improvement on both memory tests, but no significant improvement on the executive tests. HRQOL was significantly reduced in two of eight domains in the group preoperatively. Postoperatively there were no such differences compared to the SF-36 reference population and scores had improved significantly in four of eight SF-36 domains.

In patients with temporal lobe ACs we have documented improvement in cognitive functions depending on inputs from the temporal lobe, but no improvement in

functions more sensitive to an intact frontal lobe function. Hence we claim to have established construct validity for CANTAB and shown that CANTAB is applicable in a Norwegian cohort.

Paper 2: Clinical validation of Cambridge Neuropsychological Test Automated Battery in a Norwegian epilepsy population

Semi-automated neuropsychological testing has over the recent years gained a position both in clinical use and research. Still its role is debated and its use is hampered by the lack of validation studies and comparisons with more traditional and well-established neuropsychological tests. Validity of CANTAB is mainly established as construct validity, *i.e.* from investigating patients with known neurologic disease or brain lesion. The aim of this study was to compare the results from CANTAB with matched traditional, neuropsychological tests when testing epilepsy patients and by doing this establish cross-tests validity for CANTAB in a Norwegian population. As a general hypothesis we expected that measures from short-time (DMS) and visual memory (PAL) tests from CANTAB would show high correlations with measures of non-verbal memory from WMS-R and that measures from CANTAB's executive test (SOC) would show higher correlations with intelligence and measures from the HRB thought to measure executive functions. We prospectively included 15 patients ≥ 16 years who where scheduled for clinically indicated neuropsychological assessment with a neuropsychologist. The patients were asked to also complete CANTAB testing during their stay in the ward. All patients were classified with or without cognitive impairment based on results from both CANTAB and results from traditional testing.

Twelve of 15 patients were classified identically based on the two different test methods. Furthermore, one measure from DMS correlated uniquely and strongly with results from Visual paired associations 1 from WMS-R. Measures from SOC correlated both with tests for visual Memory, General Memory, Full Scale IQ and Performance IQ. Results from PAL revealed the most complex correlations: Verbal,

Visual and General Memory indexes and in addition Paired Associations and Visual Memory Span (backwards), Trail Making Test B and Visual IQ. This indicates that DMS is a unique test for visual matching to sample and hence depending mainly upon the temporal lobe. SOC depends both on memory and reasoning and PAL is a complex task demanding both the use of different memory skills and intelligence. Even though SOC is regarded an executive test, we found that several memory aspects also correlate with this test. Still Performance IQ shows the strongest correlation. Thus, SOC is not completely independent of temporal lobe function, but the test is mainly dependent on an intact frontal lobe. The strong correlations between several memory tests and PAL may reflect the dependency on temporal lobe function. We consider this a criterion validation of CANTAB in a Norwegian epilepsy population.

Paper 3: Cognitive dysfunction and health-related quality of life after cardiac arrest and therapeutic hypothermia

Improved hospital survival to over 50% after OHCA with modern treatment protocols, including therapeutic hypothermia, has lead to increased focus on functional outcome in these patients. 75-100% of the survivors after OHCA survive with a good functional outcome, i.e. CPC 1-2. In this study we wanted to investigate cognitive functions and health-related quality of life in OHCA survivors with CPC 1 or 2 one year or more after hospital discharge. We retrospectively included 26 OHCA survivors (23 males and 3 females) from two Norwegian centers who offered modern post-cardiac arrest treatment including TH. Median age was 61.5 years (range 22-79). All patients were screened with MMSE and 24 patients were subsequently tested with CANTAB. Twenty-five patients filled in SF-36 for evaluation of HRQOL.

A total of 13/25 (52%, CI: 31-73%) patients were classified as having cognitive impairments. One patient scored < 24 on MMSE and 12/25 patients had cognitive impairments according to CANTAB testing. In this study the OHCA group scored significantly lower than the CANTAB reference population on cognitive tests

assessing executive function and spatial memory. There was no significant difference in HRQOL between the OHCA group and the SF-36 reference population. We found no significant relationships between age, HRQOL, time since OCHA and cognitive function. Our results indicate that cognitive dysfunction is common in OHCA survivors even though they report normal HRQOL. The most commonly reported cognitive dysfunction after CA in general is memory disturbances and executive dysfunction. Especially deficits in short-time memory are often reported after CA. Our patients did not score worse than the integrated reference population on the test of short-time memory, but significantly worse regarding spatial memory. We were able to reproduce executive dysfunction reported by other authors. Twelve of the patients with MMSE ≥ 24 were classified as having a cognitive dysfunction. This indicates that CANTAB can reveal more subtle changes in cognitive function than MMSE. CANTAB proved able to discover cognitive dysfunctions in OHCA survivors and it was possible to use it in a CA survivor cohort.

Paper 4: Cognitive impairments after critical illness – incidence and consequences

This study focused on the effect of critical illness on cognitive function. The main aim was to estimate the incidence of cognitive impairments in patients discharged from our ICU immediately after discharge and after three and twelve months. Secondarily we looked for predictors of adverse cognitive outcome and wanted to analyse how being cognitively impaired would correlate with mortality, morbidity and health related quality of life. To isolate the effect of being critically ill on cognitive function, we excluded all patients with known pre-ICU cognitive impairments or who had an increased risk of having cognitive impairments before admittance. In addition all patients with present brain injury, brain disease or known cerebral complications were excluded. We also recruited a surgical comparison group consisting of patients who had gone through major surgery, to compare level of cognitive performance with the ICU patients. During a period of 14 months we prospectively included 55 ICU patients. After discharge from ICU, 18 of 28 (64%)

patients had a cognitive impairment according to Jackson's criteria. Twenty-seven patients were not possible to classify because they did not complete CANTAB. The incidences of cognitive impairments at 3 and 12 months were 11% (95% CI: 0-23%) and 10% (95% CI:-1-21%), respectively. The ICU patients scored worse on eight out of ten measures, but only significantly on one, compared with the surgical control group. In the ICU patients, level of cognitive performance was reduced in all tested cognitive domains (short-term memory, executive function and visual memory) at discharge compared to a normal reference population. At three months only scores on memory tests were reduced; at twelve months the ICU group scored significantly worse on only one of twelve measures. We found no associations between ICU related cognitive impairment and mortality, morbidity, HRQOL or any aetiological factors. Our results indicate that cognitive impairments are common after discharge from ICU even in patients with no known pre- or in-ICU elevated risk of such impairment. This may indicate an effect of critical illness *per se* on cognition.

5. Discussion

5.1 Summary of main findings

CANTAB tests have been demonstrated to have construct validity in Norwegian arachnoidal cyst (AC) patients

CANTAB tests and CANTAB's reference population have been cross-test validated in a Norwegian epilepsy population

Our established CANTAB test battery and applied criteria reproduced incidences and described cognitive impairments in ICU patients comparable to previous studies

CANTAB proved feasible in neuropsychological testing of survivors of critical illness

Cognitive impairments are common after cardiac arrest treated with therapeutic hypothermia, but are not associated with health related quality of life

Cognitive impairments is common after critical illness in general

After discharge, the incidence of cognitive impairments in patients with no known pre-ICU or in-ICU risk of such impairments is quite high (64%), but drops rapidly at three and twelve months to 11% and 10 %, respectively

Being critically ill may in itself cause cognitive impairment

We found no associations between pre- and in-ICU factors and the development of cognitive impairments

Cognitive impairments were not associated with mortality, morbidity or HRQOL

5.2 Cognitive dysfunction after critical illness

5.2.1 Brain dysfunction in general – terminology and classification

Damage to, or affection of, the critically ill patient's brain can have both primary and secondary causes. The affection may be focal or global and span throughout the whole register of severity: brain death, permanent vegetative state, locked-in syndrome, hemi-paresis, aphasia, delirium or cognitive impairments. The conditions may be chronic and irreversible or acute and fully reversible. Brain damage can arise secondary to primary insult to the brain or primary disease in other vital organs. In an updated article by Stevens and Nyquist [28], the authors focus on classification of brain dysfunction, aetiology and possible outcomes. They emphasise the importance of rationalising and systematising the terminology and the diagnostic approach. Their main objective is the global alteration in cognitive function seen in many critically ill patients. Stevens and Nyquist recommend that the spectrum of such brain dysfunction seen during or after critical illness is described as coma, delirium or cognitive impairments. This facilitates a systemised approach both regarding diagnosis, treatment and prognostic evaluations. Below, I will discuss further the classification of Stevens and Nyquist.

Coma

Coma is characterised by a severe disruption in wakefulness or awareness [28]. Stevens and Nyquist agree with Aristotle that awareness is the content of consciousness and depends on several cognitive skills such as perception, attention, memory and executive function. The clinician can make use of the Glasgow Coma Scale (GCS) when approaching the unconscious patient [29]. GCS is validated in several patient populations and are widely used for expressing patients' level of consciousness. GCS below 8 is regarded being in a comatose condition.

Delirium

In delirious patients, consciousness is altered, but some degree of wakefulness and awareness is kept. Delirium is further characterised by a general cognitive

impairment, confusion, altered attention, fluctuating course and disorganised thinking [30]. Delirium can be expressed both as a hyperactive delirium in an aggressive patient or as a hypoactive delirium where the patient is in a state of apathy. Confusion assessment method for the intensive care unit (CAM-ICU) is a validated tool for diagnosing ICU related delirium [31].

Cognitive impairment

Patients with isolated cognitive impairment during or after critical illness are fully alert and conscious. Their impairment is often not suspected by the ICU team unless in very grave cases where patients show signs of disorientation or confusion. The main aspect distinguishing delirium and cognitive impairment is consciousness, which fluctuates in delirium but is intact in cognitively impaired patients. Isolated cognitive impairments are more likely to be discovered days, weeks or even months after discharge from the ICU. If a cognitive impairment is suspected or if the clinician wants to screen for such impairment, MMSE [21] is the most used validated tool. MMSE is however a gross measure of cognitive function and may not reveal more subtle changes; nor can it describe the affected cognitive domain precisely.

Several and different specific conditions or diseases that may cause ICU related brain dysfunctions have been described, such as septic encephalopathy, ICU psychosis, acute organic reaction and cerebral insufficiency. These terms link aetiology and clinical presentation, which may limit their use. The terms recommended by Stevens and Nyquist focus on clinical presentation solely.

To make the delirium diagnosis some observational time is demanded to determine fluctuation in consciousness, but otherwise GCS, CAM-ICU and MMSE can rapidly give the diagnosis bedside in most cases. It is important to emphasise that other diagnoses involving brain dysfunction, such as dementia, including Alzheimer's disease, cannot be diagnosed in an ICU setting. The dementia diagnosis demands long follow-up time and also depends on activity of daily life, which is not possible to assess during the acute, critical phase. On the other hand pre-clinical variants of the

conditions mentioned above may be revealed during critical illness, thus making them relevant during follow up and rehabilitation.

5.2.2 Aetiology and epidemiology of cognitive impairments – predisposing and precipitating factors

As with other organ dysfunctions developed during critical illness the aetiology of brain dysfunction in general, and cognitive impairment in particular, is believed to be multifactorial. It is common to sort risk factors or possible causes for developing brain dysfunction such as delirium and cognitive impairment into pre-ICU (predisposing) factors and in-ICU (precipitating) factors indicating the importance of the patient's health condition before admittance to the ICU [32, 33]. Generally, there is more evidence of the impact of pre-ICU factors on brain function than of in-ICU factors, especially between severe brain dysfunction, such as delirium, and pre-ICU factors. There is strong evidence for an increased risk of delirium in patients with pre-existing dementia, advanced age, use of psychopharmacological drugs, sepsis, mechanical ventilation, heart-failure, and other conditions [34]. These associations are less strong for cognitive impairment, but it is nevertheless believed that delirium and cognitive impairments share several aetiological and risk factors. This is underlined by the fact that delirium during ICU stay increases the risk of sustained cognitive impairment also after ICU discharge [28].

Pre-ICU factors

Previous studies have established the association between pre-ICU factors and adverse cognitive outcome: gender (male>female), low functional status, lower educational achievement, malnutrition, cardio-vascular disease, previous brain injury/disease, medical disorders, drug/alcohol abuse and pre-existing cognitive impairment [32]. When controlled for other factors, age has not previously been isolated as a predisposing factor for cognitive impairment alone, cognitive impairment strikes ICU patients in all ages. The risk of having other predisposing conditions increases with age and this might explain the fact that cognitive

impairments are more common in elderly than in younger ICU patients. Some patients have subclinical conditions of dementia or other brain disorders prior to admittance to the ICU. Such conditions may also predispose for the development of cognitive impairments or the underlying condition may fully reveal during or after critical illness.

We found no association between any etiologic factor and the development of cognitive impairments. As claimed by other authors [28] it will probably demand larger multi-centre studies to reveal predictors for cognitive impairments in general, not only the severe forms. It is therefore possible that we miss such associations because of the relatively low number of patients tested.

In-ICU factors

Regarding in-ICU factors several aetiological contributors are suspected: CNS disease, hypoxemia, hypo-perfusion, infection/sepsis, sedatives/neuroactive pharmacological agents, metabolic derangement, systemic inflammation, glucose dysregulation, mechanical ventilation and several others [7, 28, 32, 33, 35]. Studies on ARDS patients have revealed that degree of hypoxemia correlates significantly with cognitive impairment [7]. Whether this applies for critical ill patients without ARDS is suspected, but not documented. The human hippocampus is regarded as being especially sensitive to hypoxia and it is known that hypoxia in the temporal lobe may cause memory deficits [36]. Thus hypoxemia, with suspected resulting cerebral hypoxia, is the most documented in-ICU etiologic factor for cognitive impairment.

It has not been demonstrated that factors describing the severity or magnitude of the disease will influence the risk of developing cognitive impairment. The factors that were explored include length of stay in ICU, duration of mechanical ventilation, APACHE II scores, days of receiving sedatives and tidal volume [32].

Effect of being critical ill on cognition

It is important to distinguish between structural brain damage caused by localised primary or secondary brain injury and diseases that may result in diffuse or scattered brain cell death and brain dysfunction. Even though structural brain damage and brain cell death will contribute to the incidence of brain dysfunction, it is possible that being critically ill in itself may have an effect on brain function. As seen above, several suspected in-ICU aetiological factors are not directly associated with brain dysfunction. Infection, sepsis, mechanical ventilation, metabolic derangement, immunological activity and other factors may possibly affect brain function with clinical manifestations, but without leaving trace of structural brain damage that are visible on routine CT or MRI scans. Meanwhile neuropathological evidence is emerging showing how both critical illness and its treatment can cause de novo cerebral atrophy. Gunther et al. describes how disrupted function in the ascending reticular activating system (ARAS) caused by sepsis, ARDS, ALI or its treatment can alter consciousness and thus contribute to the explanation of ICU delirium [37].

By excluding patients with known brain injury/disease, known brain dysfunction, or increased risk of developing such dysfunction, it is possible to explore the effects on cognition of being critically ill. We found significant differences between the ICU patients and a normal population as well as a surgical reference group. There was only significant difference between the ICU group and the surgical group on one result from CANTAB testing, but a trend towards poorer scores in the ICU group (table 3).The surgical control group had significantly higher co-morbidity and age than the ICU group. Exclusion criteria were the same in the two groups. Increasing age and co-morbidity predicted reduced level of cognitive function in ICU patients.

Table 3: Level of cognitive performance in ICU and surgical patients with MMSE ≥24, as revealed by 4 different CANTAB tests.

	ICU group at ICU discharge		Surgical group, 1-7 days postoperatively		
CANTAB test/*measure*	n	Mean (SD)	n	Mean (SD)	p(I/S)
MOT					
Mean Latency	50	-0.93 (1.33)	23	-0.72 (0.84)	0.481
DMS					
Mean correct latency	50	-1.25 (1.98)	21	-0.32 (1.06)	0.045*
Total correct	50	-0.82 (1.63)	21	-0.21 (1.10)	0.124
Percent correct, 0 sec	50	-0.33 (1.41)	21	0.06 (1.01)	0.252
Percent correct, 12 sec	50	-0.65 (1.30)	21	-0.16 (1.01)	0.123
SOC					
Problems solved in minimum moves	33	-0.48 (1.11)	18	-0.29 (1.00)	0.544
Mean moves, 5 moves	33	0.40 (0.89)	18	0.77 (1.10)	0.198
Mean subsequent thinking time, 5 moves	33	-0.93 (2.44)	18	-1.19 (2.36)	0.072
PAL					
Total errors adjusted	17	-2.10 (3.89)	17	-1.63 (3.05)	0.699
1st trail memory score	19	-1.18 (1.86)	17	-0.74 (1.55)	0.451

p(I/S): Comparison of level of cognitive performance between the surgical end the ICU group. Paired-sample t-test.

Incidences of cognitive dysfunctions in ICU patients

The incidences of brain dysfunctions in general and delirium and cognitive impairments especially vary greatly between different subgroups of critically ill patients. In general ICU cohorts it is reported that up 80% of patients are delirious at some time during their ICU stay [34]. Cognitive impairments are reported to range between 25% and 80% in different ICU cohorts. Selected studies documenting these incidences are summarised in table 4 [7, 38-43].

Table 4: Incidences of cognitive impairments in different patient cohorts evaluated at different points of time

Author	Patients	During ICU	Before/at hospital discharge	2-6 months after ICU	> one year after ICU
Hopkins et al, 1999 [7]	ARDS		100%		78%
Hopkins et al, 2005 [44]	ARDS		70%		45-47%
Sukantarat et al, 2005 [42]	General ICU			35%	
Jones et al, 2006 [40]	Mechanical ventilated, non delirious patients.	100%	50%	50%	
Cronberg et al, 2009 [38]	Cardiac arrest				50%
Rothenhausler et al 2001 [41]	ARDS				23.9% (6 years)
Jackson et al 2003 [39]	Medical ICU			32%	

From these previous reports it is reasonable to assume that cognitive impairment is common after critical illness. The trend in these results is that cohorts with patients who suffered from ARDS or were in need of respiratory support both showed high incidence of cognitive dysfunction during their stay in ICU and had the highest prevalence of chronic cognitive impairment. Patients examined after cardiac arrest had also high prevalence of such impairment more than one year after the incident. This indicates that patients with hypoxemia [7, 41], increased risk of hypoxemia [40], or increased risk of cerebral hypo-perfusion [38, 43] are at greater risk of developing cognitive impairment, thus underlining the aetiological role of hypoxia. The two studies including medical and surgical ICU patients in general [39, 42] had the lowest incidences of cognitive impairment. Based on results from these studies it is possible to argue that patients with hypoxemic aetiology are more likely to develop chronic cognitive impairment.

Our results emphasise these perspectives. The incidence of cognitive impairments in the ICU group was high immediately after discharge (64 %) but dropped rapidly to 11

% after three months indicating that cognitive impairments disappear in most general ICU patients after ICU discharge. In our CA group, where inclusion and exclusion criteria were the same and which was tested with the same CANTAB battery, incidence of cognitive impairment was 52 %. Age difference between the CA and ICU group was significant (61.5 vs 51.3 years respectively, *p-value: 0.018*). Anyhow, age alone cannot account for the major difference in incidence of cognitive impairments at 1-2 years after CA or ICU discharge. The other major difference between these groups was the confirmed episode of cerebral hypo-perfusion with possible resulting cerebral hypoxia in the CA patients while such an incident is less likely for the ICU patients. We believe this supports the aetiological role of hypoxia. Cognitive deficits that are present one year after the incident are regarded permanent [45]. Some authors claim that deficits become permanent even earlier [46]. The difference in incidences from these two cohorts indicates that patients who have suffered from cerebral hypoxia are more likely to develop permanent cognitive impairment.

When former ICU patients have such a high incidence of cognitive impairments at discharge that subsequently drops significantly already after three months, this observation may indicate that cognitive impairment in general ICU cohorts is not caused by cerebral hypoxia alone and that there are other aetiological factors, as suspected by other authors [32].

5.2.3 Cognitive impairments and outcome

Mortality and morbidity

In the study on former ICU patients we investigated mortality and one morbidity factor; institutionalisation. We found no differences in these adverse outcomes between patients with or without cognitive impairments. Are cognitive impairments then without consequences? POCD is not an identical condition to cognitive impairments after critical illness, but the two conditions are comparable. In addition to institutionalisation several POCD studies also have evaluated postoperative length

of stay, costs, hospital length of stay and medical complications. Most research on POCD includes also non-delirious patients with MMSE < 24. Perhaps some of the differences regarding mortality and morbidity between POCD and our studies can be explained by the fact that the POCD group contains more cognitively impaired patients, but it is also possible that this is caused by study strength since referred POCD studies assessed more patients than we did. Studies on cognitive impairment after CA have also concluded with negative effects of cognitive impairment on morbidity. Again these studies include more cognitively impaired patients and also more patients, but they also assess more numerous adverse outcomes such as employment status, dependency on social benefits and functional level [38].

Patients with MMSE ≥ 24 are described as having a normal general cognitive function. The cognitive impairments documented in our study include subtle changes that probably are most relevant regarding complex tasks. Hence it is possible that these changes affect groups of patients in different ways. Most CA patients and ICU patients are in the upper age groups and therefore retired or unemployed after CA or ICU stay. Perhaps these patients to a lesser degree are exposed to tasks in daily life which are affected by subtle cognitive changes. This underlines the importance of including information of pre- and post-critical illness level of education, functional status, and employment status when assessing such possible adverse effects of cognitive impairment in different patient groups.

HRQOL

Even though we documented a cognitive impairment in more than 50% of the CA patients' HRQOL was normal in the CA group compared with a Norwegian reference population. This is in accordance with previous studies on HRQOL in CA cohorts where it is documented that most of the improvement occurs during the first year after the CA [46] and that CA patients is quite similar to the normal population after one year [46-48]. There was no correlation between HRQOL measured with SF-36 and measured level of cognitive performance in our findings. Even though former ICU patients show reduced quality of life compared with the normal population both at 3 months and 12 months follow-up, there was no correlation to the level of

cognitive performance in this group either. We could not document any effect on HRQOL of having cognitive impairments after having been critically ill.

5.2.4 Types of cognitive functions that may be affected after critical illness

Previous investigations of cognitive function in these patient groups have been performed with a large variety of different cognitive tests and test batteries. The cognitive approach also differs in timing of testing, the follow-up intervals and the complexity of test batteries. When reviewing the relevant literature, it is difficult to discover an obvious or simple recipe for the cognitive approach, however some common features are revealed.

Research on hypoxic brain injury has often focused on memory deficits and on hippocampal damage. Thus, it is well documented that memory deficits and temporal lobe affection may follow from hypoxic or anoxic brain injury [49-51]. Executive functions have also been evaluated in several cohorts of patients with hypoxic brain injury, but not to the same extent as memory. Even so, executive dysfunction and behavioural changes have been revealed as a common cognitive deficit after cerebral hypoxia, often in combination with memory deficits [49, 51]. Executive dysfunction is often linked to frontal lobe affection, and it is claimed that hypoxic injury can cause “frontal lobe syndromes” explaining behavioural changes [52]. Several authors also emphasise the deterioration in visuospatial skills, which indicates possible parietal affection after hypoxic events [36, 49, 52]. When memory deficits are further explored both verbal and visual memory impairments are discovered [51]. Immediate memory and recognition memory seem to be lesser affected than delayed memory [49, 51-53].

The dominance of memory disturbances among reported cognitive impairments after critical illness is most likely due to the fact that this is the most investigated cognitive domain, not necessarily the most affected domain [54].

Research focusing not only on hypoxia, but on other aetiological factors such as critical illness and CA shows similar patterns. A hypoxic mechanism is believed to be the cause of the well-documented cognitive impairments arising after the CA. Even though investigated in different ways and with different methods, memory impairments, various executive deficits and also motor/speed deficits are often reported after CA [47, 55-57]. Also in CA patients, memory impairments seem to be the most robust finding [38, 48, 58]. Delayed recall was one of the most frequently reported sub-categories of memory impairment [48].

Regarding critically ill patients in general several types of cognitive impairments and affection of several domains have previously been reported [54, 59]. Memory and executive functions are the most investigated cognitive domains, even though several other deficits such as attention, planning, mental processing speed, language and visuospatial abilities also have been investigated and reported to be affected [7, 32, 40, 42, 48].

In our two studies on critical illness survivors we assessed motor speed, delayed memory, immediate memory, forced decision-making, visual memory, spatial memory and executive functions. As documented, both SOC and PAL are complex tests where achievements depend on several sub-functions. Considering the ICU and CA studies together, we found reduced cognitive level of performance in all domains except for immediate memory (DMS, 0 seconds delay). Immediate memory is earlier documented to be less affected than delayed memory in post-ICU or anoxic cohorts. Our finding agrees with this statement. Our results also confirm the complexity in cognitive impairments arising after critical illness. It is quite possible that more tests on other cognitive domains would have revealed even larger diversity in cognitive impairments.

5.2.5 Confounding factors regarding cognitive impairments caused by critical illness

We aimed to exclude patients with pre-ICU increased risk of cognitive impairments. Patients with severe psychiatric disorders were not included due to increased risk of

cognitive impairments. On the other hand we have not assessed the ICU group or CA group for psychiatric disorders that may have emerged after critical illness. It is previously documented that both CA and ICU survivors have higher prevalence of depression and anxiety believed to be caused or triggered by having had a critical illness [38, 60]. In addition, these patients are at risk of developing post-traumatic stress disorders (PTSD) [61, 62]. All these conditions (anxiety, depression and PTSD) can be accompanied by a reduced level of cognitive function. We did not search for these conditions in our cohorts; it is therefore possible that they partly can explain some of the documented reduced level of cognitive performance. Even so, these are also consequences of being critically ill. As with other possible etiological factors (sedation, inflammation, sepsis) we did not look for the individual factor itself, just the aggregated effect of critical illness on cognition.

Many patients will be in continuous need of analgetics and sedatives after discharge from the ICU. The use of opioids, alpha-2 agonists or benzodiazepines after ICU can affect performance on cognitive tests [63, 64]. In addition, the possibility exists that patients with renal or hepatic failure still are under the influence of both opioids and benzodiazepines, or their active metabolites, long after the ICU stay.

5.3 Validity of CANTAB

5.3.1 General perspectives on test validity

There is no unambiguous definition of validity. Validity usually refers to to what extent a measurement generated from a study or a test represents the real world. The meaning of validity also varies depending on the context. In experimental studies, validity is often described in to ways: 1. External validity, which expresses whether the results can be transferred or generalised. 2. Internal validity addresses study design, how measures were conducted, accuracy in data collection, what was/was not measured, or if there are other possible explanations for any causal relationships found. Hence when applied here, validity concerns aspects of the study in itself.

In this thesis another use of the term “validity“ is more relevant. In psychometrics (psychological testing) validity refers to the test validity, i.e. to which extent the applied test actually measures and further describes the feature under investigation. Traditionally, several types of test validity have been described; among them construct validity and criterion validity, concepts that are discussed below.

Construct validity seeks agreement between a theoretical concept, or a construct, and a specific measuring device or procedure. Based on theory and empirical data, a construct is established. This construct then represents the theoretical explanations of how and why this procedure should measure the functions approached and which results one could expect. If the postulated results are documented or the results are in accordance with theory, construct validity is established. Both confirming the tests ability to correct measure the wanted feature (convergent validity) and the tests failure to detect other features (discriminant validity) are of interest when validating psychometric tests.

With criterion validation a criterion is defined as a representative of the construct. This criterion can be described as a “gold standard”. To validate the test results, the test under investigation can be compared with the results from the representative test, i.e. the criterion. If the criterion test and the investigated test are carried out simultaneously and the results correspond, concurrent validity is established. Pearsons correlation coefficient is one statistical analysis that may be used to look for agreement between the investigated test and the criterion.

This categorisation of test validity into different separate types of validity has over the recent years been challenged by another approach to validity. The concepts of construct validity and criterion validity are still relevant, but are now viewed more as two of several contributors to the validity of a test. A test is not regarded thoroughly validated unless several of the features of validity are documented; it is not sufficient to establish only one aspect of validity.

5.3.2 Previous validation of CANTAB

Several validation studies have been performed with CANTAB. Cross-test validation/concurrent validation has been performed with some of the CANTAB tests and traditional neuropsychological tests such as Wisconsin card sorting test, Wechsler memory scale-revised and Digit span forward [65-67]. Generally, correlation coefficients are acceptable, but not all CANTAB test are validated in this way and the role of automatic test batteries such as CANTAB are debated because such validation studies are sparse [67]. Several studies have focused on construct validity of CANTAB. CANTAB is used to examine patients with different CNS profiles. CANTAB has proved able to detect neuropsychological deficits that were to be expected from the patients' CNS disease or damage. Studies on patients with excisions of the temporal or frontal lobes, or who have been subject to amygdalo-hippocampectomy, have given researchers information on how these structural changes may affect performance on several CANTAB tests [12, 16, 17]. In addition, CANTAB has been used to evaluate patients with neurological and neurosurgical disorders such as Huntington's disease [68], Parkinson's disease [69], Alzheimer's disease [70], stroke [5], head injuries [6] and normal pressure hydrocephalus [71].

Factorial validity concerns the scales of measurements used to describe function. By applying the test on a large, presumably healthy, normal population baseline data is gathered allowing for direct comparison between reference population and groups under investigation. These baseline data has been obtained through large factor analytic studies on children, adults and the elderly [72-74] in addition to be applied on more than 2000 normal controls to establish the integrated normative database [75].

The main challenge in our research is that CANTAB has not been documented in the Norwegian population and that its use in critically ill patients is limited. In addition, several of our tests have not been cross-test validated with traditional neuropsychological tests and the test battery is weakened by the fact that the reference population is English. We needed to address these issues.

5.3.3 Test-retest correlations - reliability

Test-retest correlations concern how much agreement there is between results from testing the same person with the same test at two different times. Low test-retest correlations indicate that factors other than those that we want to explore also affect the results. High test-retest correlation indicates high reliability of the test.

Composing reliable tests batteries and choosing robust and relevant results to report is a challenge. These considerations are especially relevant when designing batteries and studies meant to measure changes over time or after therapeutic interventions. A study by Lowe and Rabbitt addresses test-retest reliability in CANTAB [15]. Tests addressing executive or frontal functions are regarded as not being very reliable because discovering and remembering strategies can improve the performance. Tests measuring metric values such as speed or accuracy are on the other hand regarded as being more reliable and often show high test-retest correlation. In this study the patients were tested and retested with an interval of four weeks.

From each CANTAB test a wide selection of results is possible to report. Not all results are relevant and some results have higher test-retest reliability. After adequate tests are chosen, the researcher can further improve robustness of the results by choosing to report result with high test-retest correlations. Test-retest correlations relevant to our battery are shown in table 2.

5.3.4 Composing the CANTAB battery for ICU patients

When composing a neuropsychological test battery, several considerations must be addressed: which cognitive domains are of interest given the questions raised, are there valid tests, and which test results are most reliable?

CANTAB has previously been used in only one study on critically ill patients. Jones et al. investigated non-delirious patients during and after ICU stay with two tests from CANTAB: DMS and SOC [40]. Cognitive impairment were documented on both tests both during and after ICU stay.

Based on earlier investigations on cognitive impairments after critical illness (see section 4.3.4), it was evident that our test battery had to include memory and executive tests. Tests for verbal memory in CANTAB are not translated to Norwegian so we had to focus on visual memory and included tests that also tested delayed memory. We included two memory tests and one executive test. This reflects both the need to focus on memory deficits and test-retest considerations.

The tests included and the reported results with test-retest correlation with study populations are listed in table 6.

Table 6: Test-retest correlation published by Lowe and Rabbitt [15] and by Camcog in the CANTAB reliability study [14] on the tests we used in our studies. Overview of reported results in the four studies where we have used CANTAB

CANTAB test/reported result	Test-retest correlation coefficient, Lowe and Rabbitt [15]	Test-retest correlation coefficient, Camcog [14]	Reported in archanoid cyst study	Reported in CA, ICU and epilepsy study
Motor screening test (MOT)				
Mean latency				*
Delayed matching to sample (DMS)				
Total correct, all delays	0.56	0.50	*	*
Mean latency, all delays			*	*
Total correct, 0 seconds			*	*
Total correct, 12 seconds	0.34		*	*
Mean latency, 0 seconds			*	
Mean latency, 12 seconds			*	
Stockings of Cambridge (SOC)				
Problems solved in minimum moves, all	0.60		*	*
Mean moves, 2 moves			*	*
Mean moves, 5 moves	0.47		*	*
Mean subsequent thinking time, 2 moves			*	
Mean subsequent thinking time, 5 moves			*	
Paired associate learning (PAL)				
Total errors, adjusted		0.68	*	*
Total trails, adjusted	0.86			CA/epilepsy
1st trail memory score	0.68		*	ICU/epilepsy
Intra-extra dimensional shift (IED)				
Stages completed		0.75	*	
Total errors, adjusted		0.40	*	
Total trials, adjusted			*	

** indicates which result were reported in the different studies*

5.3.5 Validation in Norwegian patients

ACs are most commonly located in the temporal lobe region [76]. Previous studies on cognition have shown that ACs may compromise neighbouring brain tissue, probably by affecting cerebral perfusion [77, 78] and further that cognitive dysfunction is reversible after surgical decompression of the cyst [79-83]. We applied a battery of two memory tests mainly assessing temporal lobe function (DMS and PAL) and two executive tests mainly assessing frontal lobe function (SOC and IED) pre- and postoperatively to patients operated for temporal ACs. We documented significant improvement in the two tests that mainly assessed temporal lobe function (DMS and PAL); no improvement was seen on the tests with lesser inputs from the temporal lobe (SOC and IED) [84]. Our findings are in accordance with other studies focusing on temporal and frontal lobe function [17, 74] and we believe that these results for the first time confirm construct validity (convergent and discriminant, respectively) of CANTAB in a Norwegian population.

Patients with epilepsy have proven to be at risk of developing cognitive dysfunctions. Such cognitive dysfunctions were explored in Norwegian epilepsy patients and traditional neuropsychological tests and test batteries were validated in this patient group [85, 86]. During a clinically indicated follow-up at the Department of neurology, HUH, epilepsy patients were tested with Wechsler memory scale-revised, Wechsler adult intelligence III, Category test, and Trailmaking B test. We applied CANTAB in the clinical mode to these epilepsy patients in order to compare these Norwegian epilepsy patients with the integrated English reference population.

The CANTAB and the traditional test battery showed high degree of agreement in the classification of cognitive impairments. Twelve of 15 patients were similarly classified as being impaired or not impaired in the 2 test batteries. Only three patients with focal cryptogenic epilepsy, generally regarded more benign than other forms of epilepsy, were classified differently by the two batteries. This might be due to lesser impact on cognition by this form of epilepsy. In addition to agreement between the two methods of classification, several significant correlations were found between CANTAB tests and traditional test assumed to probe similar functions (Pearson

correlation coefficient). This observation adds strength to our assumption that CANTAB can be used to evaluate Norwegian hospitalised patients.

5.3.6 Summary of validation studies and recommendations for the use of CANTAB

Do the results from these to validation studies correspond with each other? The AC study establishes DMS and PAL as tests that depend on intact temporal lobe function. This is confirmed by the epilepsy study, but these tests also seem to a certain degree to be dependent on frontal function. Our results thus seem to be corresponding with emerging knowledge of cognitive functions: these functions are multi-dimensional and difficult to describe using few factors. The epilepsy study shows that both DMS and PAL are memory tests, but also that DMS tests visual memory while PAL is more complex and investigates memory in general.

The only executive test evaluated in both studies is SOC. By not being sensitive to decompression of ACs in the middle fossa, we concluded that SOC depends more on frontal lobe inputs. Again the epilepsy study presents nuances to this feature by revealing that several aspects of memory are of importance for normal function, also on SOC. As with other executive tests, SOC shows complexity and the frontal involvement is documented, hence we claim that SOC is a test of executive function.

During this project we have gained clinical experience using CANTAB. The cognitive domains addressed seem relevant, but we claim that results reported should be those showing the highest reliability. Based on this we make the following recommendations for using CANTAB when assessing ICU survivors (table 7). These recommendations are based on cognitive domains of interest in the former ICU patient, test-retest correlations, time restrictions and the Jacksons criteria.

Table 7: Proposed CANTAB tests and reported results for investigating ICU patients

CANTAB test/reported result	Test-retest correlation coefficient, Lowe and Rabbitt	Test-retest correlation coefficient, Camcog	Approximate duration of test (minutes)	ICU patients when Jackson criteria is applied
Motor screening test (MOT)			3	
Mean latency				*
Delayed matching to sample (DMS)			10	
Total correct, all delays	0.56	0.50		*
Mean latency, 0 seconds				*
Mean latency, 12 seconds				*
Stockings of Cambridge (SOC)			10	
Problems solved in minimum moves, all	0.60	0.64		*
Mean moves, 5 moves	0.47			
Mean initial thinking time		0.69		*
Paired associate learning (PAL)			10	
Stages completed		0.87		*
Total trails, adjusted	0.86			*
1st trail memory score	0.68			*
Intra-extra dimensional shift (IED)			7	
Stages completed		0.75		
Total errors to ED shift	0.70			
Reaction Time (RTI)			5	
Movement time		0.73		*
Spatial span (SSP)			5	
Span	0.64	0.60		

6. Conclusion

1: Cambridge Neuropsychological Test Automated Battery is fully applicable in an intensive care setting and also in the follow-up of such patients. CANTAB can be administered by instructed ICU personnel.

2: Three tests from the CANTAB battery (PAL, DMS, and SOC) are construct validated as well as cross test validated in Norwegian hospitalised patients showing that these tests target cognitive functions as previously described in other populations.

3: Applied criteria for classification of cognitive impairment based on results from CANTAB proved relevant when approaching groups of critical illness survivors.

4: Cognitive impairment is common after critical illness, both in cardiac arrest survivors and general ICU survivors.

5: When interpreting differences between ICU patients on one side and CA patients and post surgical patients on the other, it is possible to claim that cognitive impairment in general ICU survivors not only are caused by cerebral hypoxia, but other factors in critical illness contribute as well. Impairment caused by such influence seems more likely to resolve.

6: We found no associations between cognitive impairments after critical illness and mortality, institutionalisation or HRQOL. We cannot therefore conclude that cognitive impairments is without consequences since we have not evaluated other adverse outcomes such as hospital length of stay, costs, employment status, functional status or dependency on social benefits.

7: ICU related cognitive impairments seem to resolve spontaneously in most patients. MMSE can be used to diagnose patients with severe cognitive impairments.

8: Our findings confirm complex affection of cognition after critical illness, but we did not find a specific pattern in cognitive impairment in our patients.

7. Further research

Brain dysfunction has been addressed in several patient populations. Postoperative cognitive decline has been thoroughly investigated [87-89] and cognitive impairment after cardiac arrest has also been described in detail [38, 48, 90]. The documentation of cognitive impairment after critical illness is not yet as systematic as for POCD or CA even though conditions such as ARDS and sepsis have been explored thoroughly and several studies also describe cognition in general ICU cohorts. Our study on ICU patients is only one way to approach this group. In the future information on other specific groups such as trauma patients or head injury patients could reveal more knowledge. It is possible to include matched control groups for all these conditions by investigating patients with the same condition but without need of treatment in an ICU.

Given the already documented knowledge of the role of pre-ICU functional level and pre-ICU level of cognitive function further research within this field should include gathering information of these aspects in patients before admission to the ICU. Further follow-up of the ICU patients should include information of employment status, dependency of social benefits and activities of daily life as described in post-CA cohorts [38]. Cognitive impairments, which do not seem to affect mortality, may affect these aspects of life.

As emphasised by other authors international multi-centre studies with inclusion of large groups of patients (>1000) could aid in retrieving more knowledge of risk factors and also of consequences of even cognitive impairments. This may again help us to develop better prognostic tools and prophylactic interventions.

One field of interest would be to explore which patients will develop permanent cognitive impairment and at which point of time during the post-ICU period the cognitive impairment must be regarded permanent. If this is revealed, efforts to prevent cognitive impairment could be targeted more precisely and perhaps more efficiently. In addition it would be easier to isolate the patients likely in need of cognitive rehabilitation and hence also easier to plan care after ICU or hospital

discharge. In the future randomised clinical trials focusing on cognitive intervention or rehabilitation could reveal potential positive benefits of such attempts.

Source of data

1. Dodd JW, Getov SV, Jones PW (2010) Cognitive function in COPD. Eur.Respir.J. 35:913-922

2. Saele K, Sonnesyn H, Svarstad E, Aarsland D (2009) [Cognitive failure in terminal kidney disease]. Tidsskr.Nor Laegeforen. 129:296-299

3. Matlin MW. Cognition 6E. 6. 2006. Weily.
Ref Type: Book, Whole

4. GRAMSTAD, A. Neuropsychological assessement of cognitive and emotional functioning in patients with epilepsy. 2006. University of Bergen.
Ref Type: Thesis/Dissertation

5. Bird CM, Cipolotti L (2007) The utility of the recognition memory test and the graded naming test for monitoring neurological patients. Br.J.Clin.Psychol. 46:223-234

6. Salmond CH, Chatfield DA, Menon DK, Pickard JD, Sahakian BJ (2005) Cognitive sequelae of head injury: involvement of basal forebrain and associated structures. Brain 128:189-200

7. Hopkins RO, Weaver LK, Pope D, Orme JF, Bigler ED, Larson-LOHR V (1999) Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. Am.J.Respir.Crit Care Med. 160:50-56

8. Nasjonal veileder for beslutningsprosser for begrensninger av livsforlengende behandling hos alvorlig syke og døende. 1. 2009. Norwegian Health Authorities.
Ref Type: Pamphlet

9. Flaatten H, Kvale R (2001) Survival and quality of life 12 years after ICU. A comparison with the general Norwegian population. Intensive Care Med. 27:1005-1011

10. Jackson JC, Gordon SM, Ely EW, Burger C, Hopkins RO (2004) Research issues in the evaluation of cognitive impairment in intensive care unit survivors. Intensive Care Med. 30:2009-2016

11. Maruff P, Tyler P, Burt T, Currie B, Burns C, Currie J (1996) Cognitive deficits in Machado-Joseph disease. Ann.Neurol. 40:421-427

12. Owen AM, Sahakian BJ, Semple J, Polkey CE, Robbins TW (1995) Visuo-spatial short-term recognition memory and learning after temporal lobe excisions, frontal lobe excisions or amygdalo-hippocampectomy in man. Neuropsychologia 33:1-24

13. Beats BC, Sahakian BJ, Levy R (1996) Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. Psychol.Med. 26:591-603

14. CANTAB reliability study. 2003. Cambridge Cognition Limited.

15. Lowe C, Rabbitt P (1998) Test/re-test reliability of the CANTAB and ISPOCD neuropsychological batteries: theoretical and practical issues. Cambridge Neuropsychological Test Automated Battery. International Study of Post-Operative Cognitive Dysfunction. Neuropsychologia 36:915-923

16. Owen AM, Morris RG, Sahakian BJ, Polkey CE, Robbins TW (1996) Double dissociations of memory and executive functions in working memory tasks following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. Brain 119 (Pt 5):1597-1615

17. Owen AM, Roberts AC, Polkey CE, Sahakian BJ, Robbins TW (1991) Extra-dimensional versus intra-dimensional set shifting performance following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. Neuropsychologia 29:993-1006

18. Petersen RC (2003) Mild cognitive impairment clinical trials. Nat.Rev.Drug Discov. 2:646-653

19. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Backman L, Albert M, Almkvist O, Arai H, Basun H, Blennow K, de LM, DeCarli C, Erkinjuntti T, Giacobini E, Graff C, Hardy J, Jack C, Jorm A, Ritchie K, van DC, Visser P, Petersen RC (2004) Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J.Intern.Med. 256:240-246

20. Jennett B, Bond M (1975) Assessment of outcome after severe brain damage. Lancet 1:480-484

21. Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J.Psychiatr.Res. 12:189-198

22. Loge JH, Kaasa S (1998) Short form 36 (SF-36) health survey: normative data from the general Norwegian population. Scand.J.Soc.Med. 26:250-258

23. Kvale R, Ulvik A, Flaatten H (2003) Follow-up after intensive care: a single center study. Intensive Care Med. 29:2149-2156

24. Kvale R, Flaatten H (2003) Changes in health-related quality of life from 6 months to 2 years after discharge from intensive care. Health Qual.Life Outcomes. 1:2-

25. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. Journal of Chronic Diseases 40:373-383

26. Vincent JL, Moreno R, Takala J, Willatts S, De MA, Bruining H, Reinhart CK, Suter PM, Thijs LG (1996) The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 22:707-710

27. Le Gall JR, Lemeshow S, Saulnier F (1993) A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. JAMA 270:2957-2963

28. Stevens RD, Nyquist PA (2008) Types of brain dysfunction in critical illness. Neurol.Clin. 26:469-86, ix

29. Teasdale G, Jennett B (1974) Assessment of coma and impaired consciousness. A practical scale. Lancet 2:81-84

30. Bruno JJ, Warren ML (2010) Intensive care unit delirium. Crit Care Nurs.Clin.North Am. 22:161-178

31. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, Speroff T, Gautam S, Bernard GR, Inouye SK (2001) Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med. 29:1370-1379

32. Hopkins RO, Jackson JC (2006) Long-term neurocognitive function after critical illness. Chest 130:869-878

33. Morandi A, Jackson JC, Ely EW (2009) Delirium in the intensive care unit. Int.Rev.Psychiatry 21:43-58

34. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE, Jr., Inouye SK, Bernard GR, Dittus RS (2004) Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 291:1753-1762

35. Iwashyna TJ, Ely EW, Smith DM, Langa KM (2010) Long-term cognitive impairment and functional disability among survivors of severe sepsis. JAMA 304:1787-1794

36. Hopkins RO, Haaland KY (2004) Neuropsychological and neuropathological effects of anoxic or ischemic induced brain injury. J.Int.Neuropsychol.Soc. 10:957-961

37. Gunther ML, Jackson JC, Ely EW (2007) Loss of IQ in the ICU brain injury without the insult. Med.Hypotheses 69:1179-1182

38. Cronberg T, Lilja G, Rundgren M, Friberg H, Widner H (2009) Long-term neurological outcome after cardiac arrest and therapeutic hypothermia. Resuscitation 80:1119-1123

39. Jackson JC, Hart RP, Gordon SM, Shintani A, Truman B, May L, Ely EW (2003) Six-month neuropsychological outcome of medical intensive care unit patients. Crit Care Med. 31:1226-1234

40. Jones C, Griffiths RD, Slater T, Benjamin KS, Wilson S (2006) Significant cognitive dysfunction in non-delirious patients identified during and persisting following critical illness. Intensive Care Med. 32:923-926

41. Rothenhausler HB, Ehrentraut S, Stoll C, Schelling G, Kapfhammer HP (2001) The relationship between cognitive performance and employment and health status in long-term survivors of the acute respiratory distress syndrome: results of an exploratory study. Gen.Hosp.Psychiatry 23:90-96

42. Sukantarat KT, Burgess PW, Williamson RC, Brett SJ (2005) Prolonged cognitive dysfunction in survivors of critical illness. Anaesthesia 60:847-853

43. Torgersen J, Strand K, Bjelland TW, Klepstad P, Kvale R, Soreide E, Wentzel-Larsen T, Flaatten H (2010) Cognitive dysfunction and health-related quality of life after a cardiac arrest and therapeutic hypothermia. Acta Anaesthesiol.Scand.

44. Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JF, Jr. (2005) Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. Am.J.Respir.Crit Care Med. 171:340-347

45. Roine RO, Kajaste S, Kaste M (1993) Neuropsychological sequelae of cardiac arrest. JAMA 269:237-242

46. Lundgren-Nilsson A, Rosen H, Hofgren C, Sunnerhagen KS (2005) The first year after successful cardiac resuscitation: function, activity, participation and quality of life. Resuscitation 66:285-289

47. Hofgren C, Lundgren-Nilsson A, Esbjornsson E, Sunnerhagen KS (2008) Two years after cardiac arrest; cognitive status, ADL function and living situation. Brain Inj. 22:972-978

48. Moulaert VR, Verbunt JA, van Heugten CM, Wade DT (2009) Cognitive impairments in survivors of out-of-hospital cardiac arrest: a systematic review. Resuscitation 80:297-305

49. Caine D, Watson JD (2000) Neuropsychological and neuropathological sequelae of cerebral anoxia: a critical review. J.Int.Neuropsychol.Soc. 6:86-99

50. Hopkins RO, Myers CE, Shohamy D, Grossman S, Gluck M (2004) Impaired probabilistic category learning in hypoxic subjects with hippocampal damage. Neuropsychologia 42:524-535

51. Wilson BA (1996) Cognitive functioning of adult survivors of cerebral hypoxia. Brain Inj. 10:863-874

52. Peskine A, Picq C, Pradat-Diehl P (2004) Cerebral anoxia and disability. Brain Inj. 18:1243-1254

53. Khot S, Tirschwell DL (2006) Long-term neurological complications after hypoxic-ischemic encephalopathy. Semin.Neurol. 26:422-431

54. Hopkins RO, Brett S (2005) Chronic neurocognitive effects of critical illness. Curr.Opin.Crit Care 11:369-375

55. Lim C, Alexander MP, LaFleche G, Schnyer DM, Verfaellie M (2004) The neurological and cognitive sequelae of cardiac arrest. Neurology 63:1774-1778

56. Tiainen M, Poutiainen E, Kovala T, Takkunen O, Happola O, Roine RO (2007) Cognitive and neurophysiological outcome of cardiac arrest survivors treated with therapeutic hypothermia. Stroke 38:2303-2308

57. van Alem AP, de VR, Schmand B, Koster RW (2004) Cognitive impairment in survivors of out-of-hospital cardiac arrest. Am.Heart J. 148:416-421

58. Grubb NR, O'Carroll R, Cobbe SM, Sirel J, Fox KA (1996) Chronic memory impairment after cardiac arrest outside hospital. BMJ 313:143-146

59. Chapman RJ, Brett SJ (2007) Cognitive dysfunction in intensive care survivors. Br.J.Hosp.Med.(Lond) 68:467-469

60. Flaatten H (2010) Mental and physical disorders after ICU discharge. Curr.Opin.Crit Care 16:510-515

61. Jones C, Backman C, Capuzzo M, Flaatten H, Rylander C, Griffiths RD (2007) Precipitants of post-traumatic stress disorder following intensive care: a hypothesis generating study of diversity in care. Intensive Care Med. 33:978-985

62. Jones C, Backman C, Capuzzo M, Egerod I, Flaatten H, Granja C, Rylander C, Griffiths RD (2010) Intensive care diaries reduce new onset post traumatic stress disorder following critical illness: a randomised, controlled trial. Crit Care 14:R168-

63. Coull JT, Middleton HC, Robbins TW, Sahakian BJ (1995) Clonidine and diazepam have differential effects on tests of attention and learning. Psychopharmacology (Berl) 120:322-332

64. Wang Y, Sands LP, Vaurio L, Mullen EA, Leung JM (2007) The effects of postoperative pain and its management on postoperative cognitive dysfunction. Am.J.Geriatr.Psychiatry 15:50-59

65. Gau SS, Shang CY (2010) Executive functions as endophenotypes in ADHD: evidence from the Cambridge Neuropsychological Test Battery (CANTAB). J.Child Psychol.Psychiatry

66. Jazbec S, Pantelis C, Robbins T, Weickert T, Weinberger DR, Goldberg TE (2007) Intra-dimensional/extra-dimensional set-shifting performance in schizophrenia: Impact of distractors. Schizophrenia Research 89:339-349

67. Levaux MN, Potvin S, Sepehry AA, Sablier J, Mendrek A, Stip E (2007) Computerized assessment of cognition in schizophrenia: promises and pitfalls of CANTAB. Eur.Psychiatry 22:104-115

68. Lawrence AD, Hodges JR, Rosser AE, Kershaw A, ffrench-Constant C, Rubinsztein DC, Robbins TW, Sahakian BJ (1998) Evidence for specific cognitive deficits in preclinical Huntington's disease. Brain 121 (Pt 7):1329-1341

69. Foltynie T, Brayne CE, Robbins TW, Barker RA (2004) The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain 127:550-560

70. Blackwell AD, Sahakian BJ, Vesey R, Semple JM, Robbins TW, Hodges JR (2004) Detecting dementia: novel neuropsychological markers of preclinical Alzheimer's disease. Dement.Geriatr.Cogn Disord. 17:42-48

71. Devito EE, Pickard JD, Salmond CH, Iddon JL, Loveday C, Sahakian BJ (2005) The neuropsychology of normal pressure hydrocephalus (NPH). Br.J.Neurosurg. 19:217-224

72. Luciana M (2003) Practitioner review: computerized assessment of neuropsychological function in children: clinical and research applications of the Cambridge Neuropsychological Testing Automated Battery (CANTAB). J.Child Psychol.Psychiatry 44:649-663

73. Robbins TW, James M, Owen AM, Sahakian BJ, McInnes L, Rabbitt P (1994) Cambridge Neuropsychological Test Automated Battery (CANTAB): a factor analytic study of a large sample of normal elderly volunteers. Dementia 5:266-281

74. Robbins TW, James M, Owen AM, Sahakian BJ, Lawrence AD, McInnes L, Rabbitt PM (1998) A study of performance on tests from the CANTAB battery sensitive to frontal lobe dysfunction in a large sample of normal volunteers: implications for theories of executive functioning and cognitive aging. Cambridge Neuropsychological Test Automated Battery. J.Int.Neuropsychol.Soc. 4:474-490

75. De Luca CR, Wood SJ, Anderson V, Buchanan JA, Proffitt TM, Mahony K, Pantelis C (2003) Normative data from the CANTAB. I: development of executive function over the lifespan. J.Clin.Exp.Neuropsychol. 25:242-254

76. Helland CA, Lund-Johansen M, Wester K (2010) Location, sidedness, and sex distribution of intracranial arachnoid cysts in a population-based sample. J.Neurosurg.

77. De Volder AG, Michel C, Thauvoy C, Willems G, Ferriere G (1994) Brain glucose utilisation in acquired childhood aphasia associated with a sylvian arachnoid cyst: recovery after shunting as demonstrated by PET. J.Neurol.Neurosurg.Psychiatry 57:296-300

78. Sgouros S, Chapman S (2001) Congenital middle fossa arachnoid cysts may cause global brain ischaemia: a study with 99Tc-hexamethylpropyleneamineoxime single photon emission computerised tomography scans. Pediatr.Neurosurg. 35:188-194

79. Gundersen H, Helland CA, Raeder MB, Hugdahl K, Wester K (2007) Visual attention in patients with intracranial arachnoid cysts. J.Neurol. 254:60-66

80. Lang W, Lang M, Kornhuber A, Gallwitz A, Kriebel J (1985) Neuropsychological and neuroendocrinological disturbances associated with extracerebral cysts of the anterior and middle cranial fossa. Eur.Arch.Psychiatry Neurol.Sci. 235:38-41

81. Raeder MB, Helland CA, Hugdahl K, Wester K (2005) Arachnoid cysts cause cognitive deficits that improve after surgery. Neurology 64:160-162

82. Wester K, Hugdahl K (1995) Arachnoid cysts of the left temporal fossa: impaired preoperative cognition and postoperative improvement. J.Neurol.Neurosurg.Psychiatry 59:293-298

83. Wester K (2008) Intracranial arachnoid cysts--do they impair mental functions? J.Neurol. 255:1113-1120

84. Torgersen J, Helland C, Flaatten H, Wester K (2010) Reversible dyscognition in patients with a unilateral, middle fossa arachnoid cyst revealed by using a laptop based neuropsychological test battery (CANTAB). J.Neurol.

85. GRAMSTAD A, Engelsen BA, Hugdahl K (2003) Left hemisphere dysfunction affects dichotic listening in patients with temporal lobe epilepsy. Int.J.Neurosci. 113:1177-1196

86. GRAMSTAD A, Engelsen BA, Hugdahl K (2006) Dichotic listening with forced attention in patients with temporal lobe epilepsy: significance of left hemisphere cognitive dysfunction. Scand.J.Psychol. 47:163-170

87. Abildstrom H, Rasmussen LS, Rentowl P, Hanning CD, Rasmussen H, Kristensen PA, Moller JT (2000) Cognitive dysfunction 1-2 years after non-cardiac surgery in the elderly. ISPOCD group. International Study of Post-Operative Cognitive Dysfunction. Acta Anaesthesiol.Scand. 44:1246-1251

88. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, Rabbitt P, Jolles J, Larsen K, Hanning CD, Langeron O, Johnson T, Lauven PM, Kristensen PA, Biedler A, van BH, Fraidakis O, Silverstein JH, Beneken JE, Gravenstein JS (1998) Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. Lancet 351:857-861

89. Rasmussen LS, Steentoft A, Rasmussen H, Kristensen PA, Moller JT (1999) Benzodiazepines and postoperative cognitive dysfunction in the elderly. ISPOCD Group. International Study of Postoperative Cognitive Dysfunction. Br.J.Anaesth. 83:585-589

90. Graves JR, Herlitz J, Bang A, Axelsson A, Ekstrom L, Holmberg M, Lindqvist J, Sunnerhagen K, Holmberg S (1997) Survivors of out of hospital cardiac arrest: their prognosis, longevity and functional status. Resuscitation 35:117-121