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COGNITIVE FUNCTIONS AFTER TRAUMATIC BRAIN INJURY A 30-YEAR FOLLOW-UP STUDY

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Mi corazón y mi alma
sólo Dios conoce
mi pena y mi alegría
el camino de mis pasos
y la estrella que a mi me guía.

Miguel Poveda

ABSTRACT

Leena Himanen

COGNITIVE FUNCTIONS AFTER TRAUMATIC BRAIN INJURY
A 30-YEAR FOLLOW-UP STUDY

From the department of Neurology, University of Turku, Turku, Finland
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Many cognitive deficits after TBI (traumatic brain injury) are well known, such as memory and concentration problems, as well as reduced information-processing speed. What happens to patients and cognitive functioning after immediate recovery is poorly known. Cognitive functioning is flexible and may be influenced by genetic, psychological and environmental factors decades after TBI.

The general aim of this thesis was to describe the long-term cognitive course after TBI, to find variables that may contribute to it, and how the cognitive functions after TBI are associated with specific medical factors and reduced survival. The original study group consisted of 192 patients with TBI who were originally assessed with the Mild Deterioration Battery (MDB) on average two years after the injury, during the years 1966 – 1972. During a 30-year follow-up, we studied the risks for reduced survival, and the mortality of the patients was compared with the general population using the Standardized Mortality Ratio (SMR). Sixty-one patients were re-assessed during 1998-2000. These patients were evaluated with the MDB, computerized testing, and with various other neuropsychological methods for attention and executive functions. Apolipoprotein-E (ApoE) genotyping and magnetic resonance imaging (MRI) based on volumetric analysis of the hippocampus and lateral ventricles were performed. Depressive symptoms were evaluated with the short form of the Beck depression inventory. The cognitive performance at follow-up was compared with a control group that was similar to the study group in regard to age and education.

The cognitive outcome of the patients with TBI varied after three decades. The majority of the patients showed a decline in their cognitive level, the rest either improved or stayed at the same level. Male gender and higher age at injury were significant risk factors for the decline. Whereas most cognitive domains declined during the follow-up, semantic memory behaved in the opposite way, showing recovery after TBI.

In the follow-up assessment, the memory decline and impairments in the set-shifting

domain of executive functions were associated with MRI-volumetric measures, whereas reduction in information-processing speed was not associated with the MRI measures. The presence of local contusions was only weakly associated with cognitive functions.

Only few cognitive methods for attention were capable of discriminating TBI patients with and without depressive symptoms. On the other hand, most complex attentional tests were sensitive enough to discriminate TBI patients (non-depressive) from controls. This means that complex attention functions, mediated by the frontal lobes, are relatively independent of depressive symptoms post-TBI.

The presence of ApoE4 was associated with different kinds of memory processes including verbal and visual episodic memory, semantic memory and verbal working memory, depending on the length of time since TBI. Many other cognitive processes were not affected by the presence of ApoE4.

Age at injury and poor vocational outcome were independent risk factors for reduced survival in the multivariate analysis. Late mortality was higher among younger subjects (age < 40 years at death) compared with the general population which should be borne in mind when assessing the need for rehabilitation services and long-term follow-up after TBI.

Keywords: traumatic brain injury, cognition, follow-up, attention, survival, magnetic resonance imaging, apolipoprotein E

TIIVISTELMÄ

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KOGNITIIVISET TOIMINNOT TAPATURMAISEN AIVOVAMMAN JÄLKEEN
30 VUODEN SEURANTATUTKIMUS

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Monet tapaturmaiseen aivovammaan välittömästi liittyvät kognitiiviset häiriöt, kuten muistin, keskittymiskyvyn ja tiedonkäsittelyn hitausoireet, tunnetaan hyvin. Vähemmän tietoa on siitä, mitä tapahtuu vammautuneille ja kognitiiviselle oirekuvalle akuutin toipumisen jälkeen. Kognitiivinen toimintakyky on joustavaa ja siihen voivat vaikuttaa geneettiset, psykologiset ja ympäristötekijät.

Tämän tutkimuksen yleisenä tavoitteena oli kuvata kognitiivisten toimintojen pitkäaikainen muutos ja etsiä tekijöitä, jotka selittäisivät tätä muutosta. Lisäksi tavoitteena oli tutkia, miten kognitiiviset oireet ovat yhteydessä tiettyihin lääketieteellisiin tekijöihin ja lyhentyneeseen elinaikaan. Alkuperäinen aineisto käsitti 192 aivovamman saanutta henkilöä, jotka arvioitiin kognitiivisen tasonlaskuasteikon (MDB) avulla keskimäärin kaksi vuotta vammautumisen jälkeen, vuosina 1966 - 1972. Etsimme 30 vuoden seurantatutkimuksessa riskitekijöitä, jotka selittivät elinaikaa ja samalla vertasimme potilaiden kuolleisuutta normaaliväestöön käyttämällä vakioitua kuolleisuussuhdetta (SMR). Kuusikymmentäyksi potilasta osallistui neuropsykologiseen seurantatutkimukseen vuosina 1998 - 1999, jolloin arviointimenetelminä käytettiin tasonlaskuasteikon lisäksi tietokoneavusteisia ja muita tunnettuja menetelmiä tarkkaavaisuuden ja toiminnan ohjaamisen arvioimiseen. Apolipoproteiini-E genotyyppi (ApoE) määritettiin ja aivojen magneettitutkimuksella tutkittiin hippokampusten ja aivojen sivukammioiden tilavuudet. Depressiiviset oireet määritettiin lyhyellä Beckin depressioasteikolla. Aivovamman saaneiden potilaiden kognitiivista suoriutumista seurantatutkimuksessa verrattiin ikä- ja koulutustason mukaan kaltaistetun kontrolliryhmän suoriutumiseen.

Kognitiivinen muutos seurannan aikana oli vaihtelevaa: osalla potilaista kognitiivinen taso heikkeni, osalla pysyi ennallaan ja osalla parani. Miessukupuoli ja korkea vammautumisikä olivat kognitiivisen tason heikkenemistä selittäviä tekijöitä. Useimmat kognitiivisen toimintakyvyn osa-alueet heikkenivät seurannan aikana, mutta semanttinen

muisti parani osoittaen hyvää kuntoutumispotentiaalia tapaturmaisen aivovamman jälkeen.

Seurantatutkimuksessa havaittu muistin heikkeneminen ja toimintaidean vuorottelua edellyttävä suoriutuminen olivat yhteydessä aivojen magneettikuvauksen tilavuusmuutoksiin, mutta kognitiivisen prosessoinnin hidastumista aivojen magneettikuvaus ei selittänyt. Magneettikuvauksessa havaituilla aivojen ruhjemuutoksilla oli vain vähäistä yhteyttä kognitiivisiin löydöksiin.

Vain muutamat tarkkaavaisuutta arvioivat menetelmät erottivat masennusoireista kärsivät potilaat niistä, joilla ei masennusoireita ollut. Samaan aikaan useimmat vaativammat tarkkaavaisuutta mittaavat menetelmät erottivat ilman masennusoireita olevat aivovammapotilaat terveistä verrokeista. Vaikeudet vaativimmissa tarkkaavaisuustoiminnoissa ovat täten verrattain riippumattomia aivovamman jälkeisistä masennusoireista.

ApoE ε4 alleeli oli yhteydessä erilaisiin muistisuoriutumisiin seurannan aikana, mutta yhteydet vaihtelivat alkuperäisen ja seurantatutkimuksen välillä. ApoE ε4 alleelin ja kognitiivisen suoriutumisen välinen yhteys tuli esiin episodisen muistin tehtävissä, semanttisen muistin osa-alueella sekä kielellisessä työmuistitehtävässä. Muihin kognitiivisiin toimintoihin ApoE ε4 alleelin läsnäololla ei ollut vaikutusta.

Vammautumisikä ja työkyvyn heikentyminen olivat itsenäisiä lyhentynyttä elinaikaa selittäviä riskitekijöitä seurannan aikana. Alle 40-vuotiaana kuolleiden potilaiden kuolleisuus oli korkeampaa kuin normaaliväestössä, mikä on hyvä ottaa huomioon suunniteltaessa aivovamman jälkeistä hoitoa ja kuntoutusta.

Avainsanat: aivovamma, muisti, kognitio, tarkkaavaisuus, elinaika, seurantatutkimus, magneettikuvaus, apolipoproteiini E

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ABBREVIATIONS

ANCOVA	Analysis of covariance
AD	Alzheimer´s disease
ApoE	Apolipoprotein E
BVRT	Benton Visual Retention Test
CI	Confidence interval
CRT	Choice reaction time
CT	Computed tomography
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
DAI	Diffuse axonal injury
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
FLAIR	Fluid-attenuated inversion recovery
fMRI	Functional Magnetic Resonance Imaging
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
GOS-E	Glasgow Outcome Scale- Extended
HR	Hazard Ratio
ICD	International Classification of Diseases, Injuries and Causes of Death
LOC	Loss of consciousness
MCI	Mild Cognitive Impairment
MD	Major Depression
MD	Mean diffusity
MDB	Mild Deterioration Battery
MMSE	Mini-Mental State Examination
MR	Mortality ratio
MR	Magnetic resonance
MRI	Magnetic resonance imaging
mTBI	Mild traumatic brain injury
MWCST	Modified Wisconsin Card Sorting Test
OR	Odds ratio
PET	Positron Emission Tomography
PPCS	Persistent post-concussive syndrome

PTA	Posttraumatic amnesia
PTE	Posttraumatic epilepsy
PWA	30 paired word associates
RCI	Reliable Change Index
RR	Relative risk
RT	Reaction time
SCAN	Schedules for Clinical Assessment in Neuropsychiatry
SD	Standard deviation
SE	Standard error
SMAST	Short Michigan Alcoholism Screening Test
SMR	Standardized Mortality Ratio
SPECT	Single photon emission computed tomography
SRT	Simple reaction time
ST	Subtraction test
TAI	Traumatic axonal injury
TBI	Traumatic brain injury
ToM	Theory of Mind
VBR	Ventricle-to-brain ratio
VT	Vigilance test
WAIS	Wechsler Adult Intelligence Scale
WMS	Wechsler Memory Scale

LIST OF ORIGINAL PUBLICATIONS

I. Himanen L, Portin R, Isoniemi H and Tenovuo O: Longitudinal cognitive changes in traumatic brain injury: a 30-year follow-up study. Neurology 2006;66:187-192.

II. Himanen L, Portin R, Isoniemi H. Kurki T and Tenovuo O: Cognitive functions in relation to MRI findings 30 years after traumatic brain injury. Brain Injury 2005;19(2):93-100.

III. Himanen L, Portin R, Tenovuo O, Taiminen T, Koponen S, Hiekkanen H, Helenius H: Attention and depressive symptoms in chronic phase after traumatic brain injury. Brain Injury 2009; 23(3): 220-7.

IV. Himanen L, Hämäläinen P, Kairisto V, Partanen A, Hiekkanen H, Portin R, Tenovuo O: Apolipoprotein E ε4 and cognitive functions after traumatic brain injury. (submitted)

V. Himanen L, Portin R, Hämäläinen P, Hurme S, Hiekkanen H, Tenovuo O: Risk factors for reduced survival after traumatic brain injury: a 30-year follow-up study. Brain Injury 2011;25(5):443-52.

1. INTRODUCTION

Traumatic brain injury (TBI) is a major cause of death and disability in adolescents and young adults in industrialized countries (Maas et al. 2000, Marshall 2000). A survivor with TBI is often confronted with alterations in his or her normal functioning, operating at the biological, psychological, and social levels. Each individual case will result in a different structural and behavioral pathology depending upon the nature of the injury and the physical forces of the impact, as well as the age, sex, genetic endowment, and experience of the individual at the time of injury (Bigler 2001).

Most of the studies on TBI sequelae have dealt with short-term follow-up. The most commonly reported cognitive disorders after TBI have been memory and concentration problems, reduced information-processing speed, and executive problems. Less is known about what happens after post-acute recovery. Earlier studies suggest that there may be exaggerations of the initial cognitive symptoms (Klein et al. 1996), or that there may be recovery of cognitive symptoms (Millis et al. 2001).

The brain imaging techniques, such as magnetic resonance imaging (MRI), have shown only modest, if any, association between cognitive sequelae, especially at the chronic stage after TBI (Hofman et al.2001). Rather than focal brain injury, it is now considered that the shared cognitive impairments are better explained by more diffuse changes that occur after TBI. The more generalized abnormalities occur due to neuro-excitatory and metabolic changes. Furthermore, it is highly likely that associations between brain atrophy as measured with MRI and cognitive functions may be better seen in some cognitive functions than in others.

Major depression (MD) is one of the most frequently reported psychiatric disorders after TBI (Bryant et al. 2010). Both MD and TBI are associated with similar cognitive impairments, but there may be differences between the attentional deficits of these conditions. Many patients continue to have depressive symptoms long after the injury, although not fulfilling the criteria for MD. In clinical work, the cognitive impairments are sometimes reported to be caused by depression without proper psychiatric, neurological, and neuropsychological evaluation. This kind of practice may lead to underdiagnose of TBIs and cause medico-legal problems.

Several studies have suggested that the Apolipoprotein (ApoE) genotype is associated with the outcome after TBI (Sundstrom et al. 2004, Ariza et al. 2006). However, a long-term outcome study of individuals with severe TBI did not find any significant

relationship with ApoE4 and cognitive outcome (Millar et al. 2003). Consequently, the relationship between long-term cognitive course and the ApoE genotype is poorly known.

Besides the known initial high risk mortality, also the late mortality of the subjects with TBI may be elevated (Harrison-Felix et al. 2009). The reasons for this are not yet understood. Some of this may be related to pre-injury factors but there are studies that have found post-injury lifestyle problems that are likely to shorten life expectancy (McMillan et al. 2007).

Gaining an understanding of the long-term cognitive course and its medical mediators, as well as of the risk factors for reduced survival is of marked clinical importance. This understanding would allow us better prognostication and more effective rehabilitation or treatment of the patients with TBI.

2. REVIEW OF THE LITERATURE

2.1 Traumatic brain injury (TBI)

2.1.1 Definition and classification

Traumatic brain injury (TBI) is a traumatically induced physiological disruption of brain function which is manifested by at least one of the following: 1. any period of loss of consciousness, 2. any loss of memory for events immediately before or after the accident, 3. any alteration in mental state at the time of the accident (e.g feeling dazed, disoriented, or confused), or 4. focal neurological deficits that may or may not be transient (Kay et al. 1993).

Traditionally, TBI has been classified as open or closed injuries, depending on the presence of disruption of the dura mater. The former is typical of gunshot wounds. Closed injuries, 90 % of all TBIs, can be both focal damage, where a localized area of brain tissue has been damaged, and diffuse, where the damage is widespread and not accurately restricted. Nowadays, it is believed that diffuse damage is generally more important than focal damage in the outcome of TBI. Diffuse damage includes brain swelling, hypoxic damage, and diffuse axonal injury (DAI). Diffuse damage is most commonly associated with acceleration/deceleration forces seen, for example, in traffic accidents.

2.1.2 Severity of TBI

The severity of injury has been assessed with the Glasgow Coma Scale (GCS) and with the duration of posttraumatic amnesia (PTA). The GCS, measuring level of consciousness, includes three categories: eyes opening (score 1-4), best verbal response (score 1-5), and best motor response (1-6) (Teasdale and Jennett 1974). The total score of the GCS ranges from 3 to 15, low scores indicating a low level of consciousness. PTA is defined as lasting up to the earliest time point after which continuous memory has returned. The Finnish adult guideline recommends the use of both GCS and length of PTA. The following categories are suggested by the Guideline: mild (GCS 13-15 and PTA <24 hours), moderate (GCS 9-12 or PTA 1 to 7 days) severe (GCS 8 or PTA > 7 days), or very severe (PTA > 4 weeks) (Adult traumatic brain injury: Current Care Summary 2008). In mild TBI several other categories have been used in the literature (Bigler 2007).

2.1.3 Epidemiology

Inconsistencies in the definition and classification of TBI, along with discrepancies in data collection, have made the epidemiology of TBI difficult to describe accurately.

Problems with TBI data collection include the fact that many individuals with mild TBI may not present to the hospital, and the ones who do present may be discharged from the emergency department without adequate documentation. It has been estimated that only 25% of the individuals with TBI are treated in hospitals (Sosin et al 1996). Severe TBI with associated death at the scene of the accident or during transport to hospital may also not be accounted for completely in data collection for TBI epidemiologic studies.

In Europe, the incidence in adults with all TBI severities, is in the range of 150-300 per 100 000 per year (Tagliaferri et al. 2006), but the incidence of TBIs varies widely. The observed variation could be partially explained by differences in the criteria used to define TBI or to identify patients. The annual incidence of TBI in Finland was 101 per 100 000 people on the basis of the hospital discharge register (Koskinen and Alaranta 2008). In the cohort study of Northern Finland, the annual incidence of TBI was 118 per 100 000 (Winqvist et al. 2007). The most recent study, with special emphasis on defining mild TBI, found a rate of 137 per 100 000 (Numminen 2010).

Altogether 15 000-20 000 new incidences of TBI occur every year in Finland and about 100 000 have persistent symptoms of TBI. It is also the main cause of death for individuals aged < 45 years. The main causes of TBI are traffic accidents, falls, and assaults (Jennett 1996). In Finland, traffic accidents are involved in 20 %, falls are responsible for 65 %, and assaults account for 5 % of all TBI cases (Koskinen and Alaranta 2008). Approximately half of all TBIs occur in males aged 15-34 years (Jennett 1996). Therefore, TBI often disrupts important periods of life in education, vocational productivity and adult independence, and beginning spousal relationships and family development.

2.1.4 The mechanism and pathophysiology of TBI

The initial insult sets in motion a sequence of pathological events that are progressive. Primary injury includes a diffuse axonal injury (DAI), hemorrhages and contusions of the brain. It is linked directly to impact and inertial forces, the anatomy of the skull, and the substance of the brain. DAI is related more to rotational acceleration forces, and translational acceleration have been associated with more local contusions (McIntosh et al. 1996). However, the term “local” may be misleading, since despite what may be visu-

alized on any contemporary neuroimaging analysis, damage to the brain will always be beyond the visually identified lesion represented on the scan (Bigler 2001).

The secondary injury occurs within minutes, hours, days and weeks after TBI and happens in 90% of the patients treated in hospitals (Miller 1993). The secondary injury is nowadays considered very important for the outcome of the patients (Chesnut 1993). Studies in models of TBI have begun to unravel the mechanisms producing secondary damage. Four categories of the mechanisms can be defined, those associated with 1) ischemia, excitotoxicity, energy failure, and resultant cell death cascades; 2) secondary cerebral swelling; 3) axonal injury; and 4) inflammation and regeneration (Kochanek et al. 2007). There are mediators in each of these categories, both damaging and neuroprotective in nature, that are poorly understood. Early hypoperfusion and ischemia after severe TBI appears to represent a finding that is seen in most cases and is associated with poor outcome. Cerebral swelling and accompanying intracranial hypertension contribute to secondary damage in two ways. Intracranial hypertension can compromise cerebral perfusion, leading to secondary ischemia. In addition, it can produce the devastating consequences of deformation through herniation syndromes (Kochanek et al. 2007).

The distinction between primary and secondary injury has been questioned. The classical view that traumatic axonal injury (TAI) occurs due to immediate physical shearing is challenged by recent experimental studies. These suggest that TAI predominantly occurs by delayed process termed “secondary axotomy” (Povlishock and Jenkins 1995).

2.2 Cognitive impairments after TBI

2.2.1 Cognition: central concepts, theories, and methods

Cognition refers to various aspects of information processing in the brain (latin: *cognoscere*, “to know”). Cognition includes processing of memory, attention, language, executive functions, visual and social information, and psychomotor functions. Most of the cognitive processes can be evaluated quite objectively with different kinds of cognitive methods or tests. In clinical settings, interviews of patients and relatives are additional important sources of information to assess any changes in cognition.

2.2.1.1 Memory systems

Human memory has been traditionally divided into two main processes basedon retention

time. Thus, sensory memory or short-term/working memory, and long-term memory have been identified. Sensory memory has a lifetime measurable in milliseconds to seconds. Working memory represents a limited-capacity store for performing mental operations and was originally proposed by Alan Baddeley and his colleagues (1974). The contents of working memory originate from sensory inputs or by retrieval from long-term memory. Working memory is assumed to comprise an attentional controller, the *central executive*, assisted by two subsidiary systems, the *phonological loop* and the *visuospatial sketchpad*.

Long-term memory consists of several subtypes. Basically, it has been divided into declarative and implicit memory. Implicit memory refers to memory processes that do not require intentional recollection of the experience. The simple classical conditioning and motor skills are examples of implicit memory. According to Tulving (1989), the declarative memory has two separate systems known as episodic memory and semantic memory. *Episodic memory* refers to our capacity to remember events and experiences of our lives. *Semantic memory* refers to conceptual knowledge of information and facts about the world without necessarily the remembrance of the episode where the knowledge was acquired. The semantic memory is thought to be organized in a hierarchical manner with different levels of conceptual knowledge (Laatu et al. 1999).

It is often useful to separate three aspects of any memory system: encoding, the processes whereby information is registered; storage, the maintenance of information over time; and retrieval. All these processes are usually covered in neuropsychological evaluation.

In more practical life, a question has been raised about the prospective memory; our capacity to remember to do something at a given time or place. Prospective memory can be time-based (eg, remembering to take medications at noon) or event-based (eg. remembering to take medications with lunch). It is, however, unclear how prospective memory works. Besides memory, prospective memory seems to require motivation and executive functions, such as strategies and planning ability (Baddeley 2004).

2.2.1.2 Prefrontal functions: executive functions, attention, and social cognition

Several function categories related to the prefrontal region have been proposed. Stuss (2007) proposed the following four functional domains within the frontal lobes to give more precise classifications (Figure 1). 1) *Executive cognitive functions* are involved in the control and direction (e.g. planning, monitoring, energizing, switching, inhibiting) of lower-level, more automatic functions. Also the distinction, into automatic and more attentional and working memory demanding processes, has been proposed earlier (Schnei-

der and Shiffrin 1977, Shallice 1982, Fodor 1983). Executive functions are believed to be mediated primarily by the *lateral prefrontal cortex*. Test performance, however, purposed to measure executive functions may be impaired after diffuse brain damage, inefficient integrative functioning, and after damage to many non-frontal brain regions. The following tests are used to measure executive functions: the Wisconsin Card Sorting test; Trail-Making tests, and verbal fluency tests. Tests of attention, such as sustained attention, inhibition of irrelevant information, monitoring of information, and variability in reaction time (RT) also fall within the category of executive functions. 2) *Behavioral-Emotional Self-Regulatory Functions.* Patients with *inferior (ventro-)medial frontal cortex* damage have difficulty in performing normally in unstructured situations, and in understanding the emotional consequences of their behavior, despite intact performance on commonly used neuropsychological tests of executive functioning. Assessment of these abilities tends to be more experimental in nature. 3) *Self-Regulation of energization and drive.* Damage to left or right *superior medial frontal* regions results in deficits in maintaining actions or mental processes. Perhaps the best measures to evaluate impaired energization are demanding RT measures. Choice RT and simple RT tasks demanding concentration strongly demonstrate the effect of pathology in the superior medial regions (Alexander et al. 2005, Stuss et al. 2005). 4) *Metacognitive processing.* Although the relationship between cognitive processes and anatomy is uncertain, the *frontal polar* region has been related to the highest of human integrative behaviors: theory of mind and self-awareness, humor appreciation, and self integrated autobiographical memory. Self-awareness implies a metacognitive representation of one's own mental states, beliefs, attitudes, and experiences. Through this self-reflection one has a key to understanding one's own thoughts and external events, and through this self-knowledge to understanding the mental states of others. It is the basis for the ability to make social judgments. The neuropsychological assessment for this cognitive domain includes different kinds of perspective-taking and Theory of Mind (ToM) tasks.

The impact of the subcortical myelinated fibers, or their TBI-related breakdown, on the pre-frontal functions, is poorly known. Some of the recent studies suggest that there may be an association between white matter disconnections and the social cognitive networks or the executive functions (Levin et al. 2011, Hartikainen et al. 2010). The subcortical myelinated fibers can be arranged into groups, including fibers interconnecting one hemisphere with the other (comissures), long and short fibers interconnecting cortical areas of the same hemisphere (association tracts), and fibers connecting the cortex with subcortical centers (projection fibers).

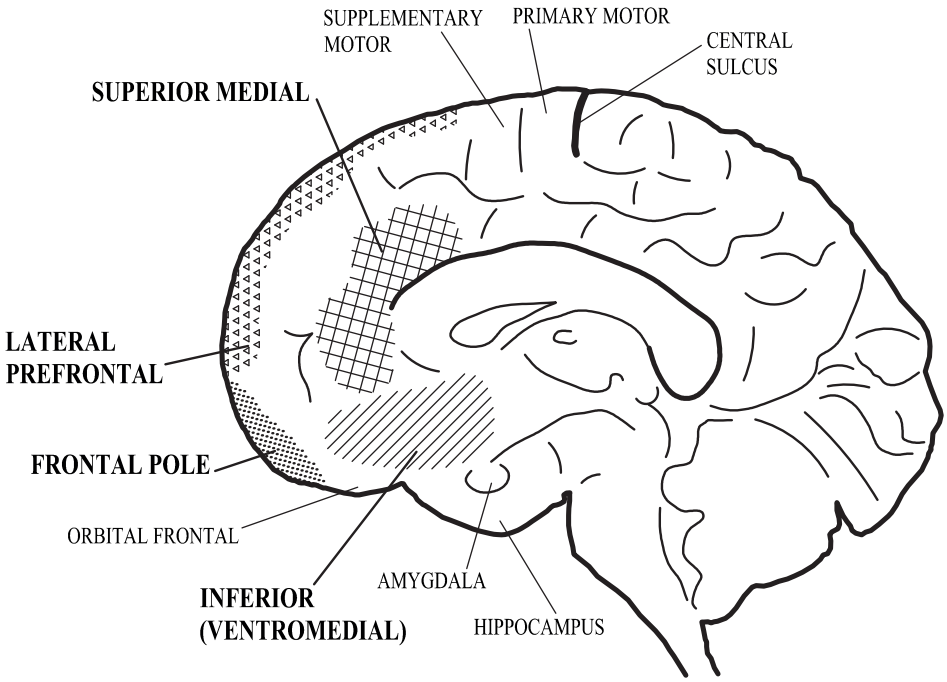

Figure 1. Pre-frontal regions involved in the four functional domains according to Stuss (2007)

2.2.1.3 Information-processing speed

Slowness in information processing is one of the most commonly reported cognitive dysfunctions after TBI. Information-processing speed is mediated by diverse brain structures that include multiple cortical regions, subcortical nuclei, and many white matter connections. The pathophysiology of TBI may affect information- processing speed in several ways.

Computerized testing methods have been widely used in sport concussions and in other mild TBI (mTBI) research (Ellemberg et al. 2009, Fazio et al. 2007, Echemendia et al. 2009). Simple reaction time tasks are often preserved after TBI, but choice or complex reaction time tasks are frequently more difficult and lead to detectable impairments (Stuss et al.1989, Ponsford et al. 1992). In a study of Zoccolotti et al. (2000), patients showed considerably more difficulty in the selective attention tasks requiring go- no go responding (combining working memory with inhibitory control) or in divided attention (increasing

the working memory load), with up to one half demonstrating deficits. These cognitive deficits may be a behavioral index of diffuse cerebral damage that subsequently limits the speed of information-processing particularly as environmental demand increases. Hence, patients with TBI must exert greater mental effort in cognitive tasks that may have been readily managed prior to injury.

2.2.1.4 Verbal and visuomotor functions

Language is best defined within the context of communication. Human communication involves the sharing and exchange of information between people. Language refers to communication through the use of words or other symbols and entails the use of multiple modalities, such as speaking, auditory comprehension, reading, writing, and gesture (Tanner 2003). In TBI, the injury mechanism (DAI) typically yields a far less homogenous array of deficits than is seen, e.g. in stroke. That is why pure aphasias are seldom seen after TBIs. Individuals with TBI frequently have communication disorders related to their cognitive deficits; attention deficits may reflect on topic maintenance and turn taking, impairments in social cognition on insensitivity to social cues (perceiving emotions and vocal prosody), and impairments in verbal abstraction on understanding humor and sarcasm. Basically, such individuals often have disorders in language use (i.e. pragmatics). Pragmatics refers to the set of rules which govern the use of language in context.

Two different pathways of visuoperceptual information processing have been proposed. The ventral or occipitotemporal pathway is specialized for object perception and recognition, for determining what it is we are looking at. The dorsal or occipito-parietal pathway is specialized for spatial perception, for determining where an object is and for analyzing the spatial configuration. “What?” and “where?” are the two basic questions to be answered in visual perception. Motor functioning is a crucial part of visual perception; they are closely linked during the developmental stages, and visual perception is used to guide our movements and goal-oriented behavior.

Although several instruments have been developed to assess verbal and visuoperceptual performance, the Wechsler Adult Intelligence Scale (WAIS) is favored by most clinicians working with patients with TBI. It gives a general profile of intellectual (both verbal and nonverbal) abilities, and some of the subtests have been employed in estimating premorbid intellectual functioning because of their robust resistance to brain injury (Eslinger et al. 2007). The Wechsler scale also provides extensive normative data that enable statistical comparisons, enhancing the strong reliability and validity indicators of

the scale. However, the special nature of TBI and its influence on verbal or visuomotor function should be taken into account. Many times these pragmatic verbal dysfunctions caused by TBI are cognitive communicative impairments, not usually reflected in verbal tests of WAIS or other language tasks focused on a single word or isolated sentences. Lower performance on performance subtests of WAIS is often related to slowed information processing rather than specific visuoperception impairment.

2.2.1.5 The screening test for general cognitive level (MMSE)

The Mini-Mental State Examination (MMSE) is the most widely used tool to assess general cognitive level in the elderly population. It takes little time to administer (5 minutes) and this makes it a practical instrument for larger patient groups. However, it is very insensitive in both TBI assessment and early stages of dementia. As for individuals with TBI, it does not include items sensitive to the TBI sequelae, that is to say, comprehensive items for memory and learning, executive functions and cognitive processing speed.

2.2.1.6 The concept of cognitive/brain reserve

Brain reserve capacity is a theoretical construct that refers to findings that postulate neuroprotective processes against central nervous system illnesses or brain traumas. Neuroprotective factors can be overall brain size, specific anatomical-functional relations, or psychosocial factors like general intelligence or education level. Vice versa, low cognitive reserve exposes an individual to more risks in the case of another insult to the brain. In TBI research, it has been suggested that an earlier TBI can lead to premature occurrence of Alzheimer's diseases (AD) (Satz 1993).

2.2.2 Cognitive outcome after mild TBI (mTBI)

There are many definitional statements regarding what constitutes a concussion or mTBI but there is a general agreement that mTBI is a consequence of a blunt impact with sudden acceleration, deceleration, or rotation of the head with a GCS of 13-15. The prevalence of mild TBI is estimated to be high, higher than published figures estimate, because most people who sustain a mild TBI are not evaluated in the emergency department or admitted to hospital (McCrea et al. 2009, Delaney 2005). This is often the case in sport-related concussions. Most individuals with mild TBI recover completely without permanent cog-

nitive or psychological sequelae (Carroll et al. 2004, Belanger et al. 2005, Iverson 2007). However, a portion of the patients do not follow this favorable course, referred to as the "miserable minority". If the symptoms last more than three months, the term persistent post-concussive syndrome (PPCS) is used. Ruff et al. (2005) and Alexander et al. (1995) have estimated that 10-20% of the individuals have incomplete recovery, making it a major public health concern. Although the science concerning mild TBI has progressed rapidly, the evolvement of an unfavorable outcome is poorly understood. Psychiatric (Ponsford et al. 2000), genetic (Dardiotis et al. 2010) and brain-structural (Bigler 2007), as well as multifactorial hypotheses (Iverson G et al. 2007) have been proposed as reasons for an unexpected outcome. A recent review on the topic concluded that concussion can lead to structural damage due to vulnerability of the upper brainstem, hypothalamic-pituitary axis, medial temporal lobe, basal forebrain, and long-coursing white matter fibers, particularly involving the corpus callosum and fornix (Bigler 2007). Symptoms of impaired attention, memory, and executive function, along with changes in emotional regulation, dominate the clinical picture of PPCS (Lundin et al. 2006).

2.2.3 Cognitive impairments after moderate-to-severe TBI

Meta-analysis of existing research demonstrates that moderate-to-severe TBI causes larger and more persistent impairment of overall cognitive functioning than mTBI (Schretlen and Shapiro 2003). Subjects with moderate-to- severe injuries frequently face a spectrum of cognitive, social, emotional, and behavioral changes from their pre-traumatic level. However, the immediate recovery is not uniform in different cognitive domains: some domains are likely to recover more quickly than others (Christensen et al. 2008).

In more severe injuries, often the immediate recovery is accompanied by unawareness of deficits known as anosognosia. The lack of awareness influences an individual's ability to acknowledge his or her cognitive and behavioral changes. Subjective evaluations of cognitive impairments may thus be unreliable sources of information. That is why more comprehensive and objective methods are needed, such as psychometric testing or interview of the individuals' significant other who has known the individual before the TBI. Problems with memory and executive functions, as well as reduced rate of information processing, are the most frequently reported cognitive dysfunctions after moderate-to severe TBI as assessed with cognitive tests.

2.2.4 Cognition and normal aging

The greatest risk factor for cognitive decline is age itself: as the life expectancy increases, so does the prevalence of cognitive decline and dementia (Bishop et al. 2010). An increasing amount of knowledge about cognitive aging has emerged during the last twenty years.

Normal aging is accompanied by many physiological changes in the brain, both structural and functional. The studies have shown that separate brain regions that interact to subserve higher-order cognitive functions show less coordinated activation with aging, suggesting a global loss of integrative function (Andrews-Hanna et al. 2007). This correlates with poorer cognitive performance in many cognitive domains. According to the frontal aging hypothesis, normal aging causes changes in the microstructure of the frontal lobes. In addition to frontal lobes, the hippocampus is a well-studied region that shows structural changes in normal aging (Raz et al. 2007). It is commonly accepted that hippocampal atrophy accompanies normal aging but to a lesser extent than in AD, although others think that no hippocampal atrophy occurs with normal aging (Folstein and Folstein 2010).

Aging does not lead to a global memory decline but rather has a differential effect on specific aspects of memory. In general, episodic memory declines with age (Craik and Jennings 1992, Nilsson 2003). Aging can also affect the encoding of new information, particularly when effortful or strategic processes are required (Daum et al. 1996). Recognition memory is less affected by normal aging than recollection, which requires more effortful processing. Semantic memory actually increases with age as individuals enrich their knowledge over the life span (Beier et al. 2001, Verhaeghen 2003). Prospective memory, in turn, declines with age (Henry et al. 2004) probably because internal cues and self-initiated processes become less reliable with increasing age.

Age-related decrements are often found on tasks requiring executive functioning processes, which is consistent with the frontal aging hypothesis. Such tasks include those assessing planning, inhibition, set shifting, and verbal fluency. One area of executive functioning on which normal aging has a greater impact is working memory. Working memory places greater demand on cognitive resources, as it requires information processing in addition to basic storage. Consistent with this, increasing the complexity of working memory tasks magnifies age-related decrements (Dobbs and Rule 1989). Sustained attention is a relatively simple attentional process that is largely unaffected by normal aging (Berardi et al. 2001), while inhibitory control, divided attention, and selective attention are more age-sensitive (McDowd et al. 1988,Verhaeghen and Cerella 2002, Gold et al. 2010).

In general, visuospatial abilities decline with age disproportionately to verbal abilities (Jenkins et al. 2000, Coffey et al. 2001). Compared to their younger counterparts, older adults demonstrate poorer performance on performance subtests than on verbal subtests of the WAIS. The reason for this decline is unclear; it may be that visual and visuospatial functions require more integrative brain processing that is more vulnerable to the aging effects, than do verbal functions.

Although language abilities are relatively unaffected in normal aging, language difficulties may arise due to reduced frontal processing. Most language problems are due to retrieval difficulties rather than a loss of semantic information (Wingfield and Kahana 2002).

Neuropsychological clinical decision-making is complicated by the fact that variability in test performance increases with advancing age (Ylikoski et al. 1999).

2.2.5 Cognition and aging after TBI

Recovery from TBI has been a study aim for decades, but most of the studies have focused either on immediate recovery or on major long-term global outcomes, such as return to work (Kreutzer et al. 2003, Nybo 2005, Olver et al. 1996, Stambrook et al. 1990) or psychosocial issues (Draper et al. 2007, Franulic et al. 2004, Koskinen 1998) or functional outcome (Ponsford et al. 2008a). It is important to acknowledge that while these outcomes are important, they are different from the information neuropsychological methods give us. The brain is the most complex organ in humans and more exact and detailed information can be reached with careful and comprehensive cognitive methods. The shortcoming with more global outcome measures is that they do not give us information about neurocognitive domains that may be especially vulnerable or, on the other hand, form the reserve for positive cognitive recovery. Without this information, rehabilitation aims can be only poorly defined.

There are only a handful of studies that have dealt with the long-term cognitive course of individuals with TBI. The studies suggested that TBI can cause permanent sequelae in specific domains of cognitive functioning and it might attenuate the age-related decline in cognitive functioning (Klein et al. 1996, Sendroy-Terrill et al. 2010). Some of the earlier studies have major methodological problems due to cross-sectional designs (Klein et al. 1996) or reliance on subjective evaluation of the cognitive symptoms (Sendroy-Terrill et al. 2010). Subjective evaluations of the cognitive symptoms can be influenced by, besides lack of self-awareness, by coping strategies, and also by mood disorders (Draper and Ponsford 2009).

A follow-up of cognitive recovery in 182 subjects with complicated mild-to-severe TBI showed that 22% improved, 15 declined, and 63% were unchanged between one and five years following injury (Millis et al. 2001). These individuals were recruited from individuals who were referred to rehabilitation, thus indicating a strong selection bias. A long-term retrospective follow-up of the intelligence of 74 individuals was conducted one year and 16 years after severe TBI in another study (Wood and Rutterford 2006). In the study (mean age at follow-up 46.7 years) no difference in intelligence was found during the follow-up time in the study group as a whole, although the cognitive decline was permanent compared with the pre-injury level. The intelligence level was associated with the education level so that the less well-educated were at greater risk of cognitive decline. Although the authors did not find evidence of an accelerated aging effect for the whole study group, they did find a small cognitive decline for the older, more severely injured individuals. One recent paper reported prospectively cognitive functions after 33 moderate-to-severe TBIs (Till et al. 2008) through repeated neuropsychological assessments over the first five years. The change was calculated using the reliable change index (RCI). Significant cognitive decline was seen on at least two neuropsychological measures in 27.3 % of the individuals. The decline was significantly correlated with hours of therapy at five months post-injury. The authors concluded that cognitive deterioration may follow an initial period of recovery but the reasons for this post-acute decline are still unclear.

Several background variables associated with long-term cognitive functioning have been proposed. Most studies have found an association between higher age at injury and cognitive impairments (Klein et al. 1996, Sendroy-Terrill et al. 2010) in adult individuals. The association between injury severity and long-term cognitive functioning has been ambiguous, some studies have found an association (Sendroy-Terrill et al. 2010, Wood and Rutterford 2006), while others have not (Klein et al. 1996). It has been proposed that PTA or GCS is more related to cognitive outcome in severe cases of TBI than in mild-to-moderate ones. If both the severity classifications have been used, loss of consciousness (LOC) and the length of PTA, the length of PTA has had a better prediction value (Ponsford et al. 2008a). Because there are only few long-term cognitive follow-up studies, the association between injury severity and cognitive outcome as assessed with standardized cognitive methods remains unclear. The association between the level of education and cognitive outcome has been reported in several studies (Ponsford et al. 2008a, Wood and Rutterford 2006), thus supporting the theory of cognitive reserve.

2.3 Cognitive outcome after TBI in relation to specific medical issues

2.3.1 Cognition and magnetic resonance imaging (MRI) after TBI

2.3.1.1 MRI findings in the chronic phase after TBI

Even though neuroimaging, such as MRI, is an important objective measure of TBI, there are several variables that have to be considered. Studies have suggested partial resolution of MRI lesions in the chronic stage so that there is a significant decrease of in the visibility of both cortical contusions and other intraparenchymial injuries (Brandstack et al. 2006). Recovery from diffuse TBI is dynamic and changing, particularly in the first year of injury. The injury type, the severity of the injury, the brain regions most likely affected, the age at time of injury, cognitive reserve, and individual differences are all variables that are involved (Bigler 2007). However, this multivariable expertise is not widely available in clinical practice and often individuals with persistent cognitive impairments lack detectable findings on conventional MRI.

Late MRI has been suggested to underestimate the extent of DAI. Hydrocephalus ex vacuo is a commonplace occurrence in moderate-to-severe TBI. One way to evaluate a diffuse injury later is to compare the ratio of total ventricular volume with the total brain volume, the so-called ventricle-to-brain ratio (VBR) (Bigler 2007). The volumes can be measured by various techniques on either CT or MR images. The VBR is calculated by dividing total ventricle volume by total brain tissue volume and multiplying that number by 100 to yield a percentage of brain volume occupied by the ventricles. From mid-adolescence to late middle life, the VBR is relatively constant at about 1.5, with a standard deviation of approximately 0.5 (Blatter et al. 1997). Following TBI-induced neuronal cell loss, brain volume is reduced but ventricular cerebrospinal fluid (CSF) pressure remains constant. There will be a natural, passive expansion of the ventricle. Hippocampal atrophy following TBI has been one of the most replicated findings in quantitative analysis of temporal lobe structures (Bigler 2007). Furthermore, the hippocampus is one of the most widely studied brain region. One of its functional roles is the storage and recall of declarative memories.

2.3.1.2 Cognitive functions in relation to MRI findings after TBI

Previous studies have correlated specific structures of the brain, as measured with MRI, and cognitive measures. In patients with AD or in patients with genetic risk for AD, the hippocampal volumes have been reported to correlate with delayed memory tasks: the smaller the volume the more impairment in memory tests (Lehtovirta et al. 1995, Killiany et al. 2002). The findings in cognitively healthy subjects are not consistent (Ylikoski et al. 2000, Hackert et al. 2002), but as the recent review of the topic concluded: brain atrophy of aging in the absence of dementia is related to vascular disease but not hippocampal atrophy (Folstein and Folstein 2010).

Some studies with TBIs have found a modest association between cognitive outcome and structural findings (Hofman et al. 2001). It is important to note that cerebral atrophy visualized by MRI does not necessarily mean decline in cognitive functions and vice versa. Due to the vulnerability of certain brain structures and the very different type of diffuse nature of the brain injury, there are some domains of cognition that are likely to correlate better than others. The index score from the Wechsler Memory Scale-revised correlated with the hippocampal volume (Tate and Bigler 2000). A study made at the subacute phase ("more than one year") after the injury found that trauma produced disproportionate white matter loss associated with increased temporal horn and sulcal cerebrospinal fluid volumes (Bigler et al. 2002). It also caused substantial hippocampal atrophy, which was related to the memory impairment. The role of the diffuse nature of pathology at the late phase after TBI has been emphasized also by another study (Reider-Grosswasser et al. 2002). While memory outcome is one of the most replicated of neurocognitive sequelae of TBI and is related to hippocampal atrophy, memory impairment following TBI can also result from wide-spread medial temporal lobe damage (Bigler 2007).

Other domains of cognitive decline that are typical after TBI, such as altered executive functioning or reduction in information processing speed, have been less frequently reported to be associated with MRI volumetric or other structural findings.

2.3.1.3 Brain imaging in TBI: recent development

One of the promising new tools to study TBI outcome is diffusion tensor imaging (DTI). A recent study found that white matter changes were negatively correlated with all the cognitive domains studied (Kraus et al. 2007). Findings on DTI have been associated with executive functioning of the fronto-striatal network in mild-to-moderate TBI (Hartikainen

et al. 2010). Severe injuries are suggested to be based on both myelin and axonal injuries, while milder injuries have mainly axonal injuries (Kraus et al. 2007). In a serial imaging study (Kumar et al. 2009), there were individuals without abnormalities in an initial phase but a significant decrease in the fractional anisotropy (FA) and mean diffusity (MD) was observed in a few regions of the Corpus Callosum, which was suggestive of demyelination/gliosis.

2.3.2 Cognitive functions and depression after TBI

Psychiatric disorders after TBI are common. While pre-injury factors may explain a part of the high incidence rate, there are undoubtedly novel cases after TBI (Bryant et al. 2010, Whelan-Goodinson et al. 2010). Furthermore, it is very common that individuals suffer posttraumatic behavioral symptoms that do not always fulfill standardized criteria of psychiatric disorders. Behavioral changes are often described in terms of loss of initiative, apathy, increased dependency, irritability or aggression, fatigue or decreased energy, emotional lability, anxiety, impulsivity, disinhibition, insensitivity to the need of others, childishness, poor judgment in social and financial matters, and either hypersexuality or hyposexuality, emotional lability, with an overall lack of insight into one's personality changes (Wood 1990). It is of note is that the individuals with diminished awareness are often unwilling to engage in rehabilitation and learn compensatory strategies to enhance adaptation to the behavioral changes after TBI.

Major depression has been the most commonly reported psychiatric disorder after TBI (Bryant et al. 2010). However, the rates of depression have varied greatly among the studies, from 9 % (Fann et al. 2004) to 77 % (Varney et al. 1987). One of the reasons for this variation may be the use of different kinds of methods to evaluate depression. Furthermore, the limited time of follow-up may partly explain the differences among the studies.

Both major depression and TBI have been associated with similar cognitive dysfunctions. Both of these conditions have been associated with reduced capacity of attention, memory and cognitive processing speed (Bashore and Ridderinkhof 2002, Farrin et al. 2003, Merriam et al. 1999, Rao et al. 2010). However, there may be differences between the two conditions. While individuals with depression and without TBI often complain about memory problems, the individuals with TBI may underestimate the cognitive disorders (Farrin et al. 2003). The individuals with major depression (without TBI) may also vary more by the extent to which they suffer from cognitive deficits than the individuals with TBI, who very often have the cognitive sequel as a rule. In psychiatric disorders,

the cognitive decline may be general to all the different psychiatric disorders, not specific. For example, working memory capacity has been reduced in many psychiatric conditions, not only in major depression. However, what has been characteristic and specifically related to major depression in relation to other psychiatric disorders is the general slowness in psychomotor speed (Sobin and Sackeim 1997, Coffey et al. 1990). It has been assumed that the severity of major depression is related to the increasing severity of cognitive dysfunction, but the results have not been consistent (McDermott and Ebmeier 2009).

The literature lacks studies that compare cognitive dysfunctions in relation to depressive symptoms after TBI. Furthermore, there are no systematic comparisons of patients with major depression and individuals with TBI in relation to cognitive functions.

2.3.3 Apolipoprotein genotypes and cognitive recovery after TBI

Considerable variability exists in outcome after TBI, which is only partly explained by known premorbid or injury- related factors. Genetic factors influencing the brain's susceptibility to injury, and its capacity for reorganization, neuronal regrowth and repair are assumed to play a part. Apolipoprotein E (ApoE) is produced by astrocytes and microglia and is responsible for the maintenance of structural integrity of the microtubules within axons. There are three different isoforms of ApoE, coded for by the ApoE2, ApoE3, and ApoE4 genes. The gene associated with ApoE influences the construction and regeneration of microtubules in an allele-specific manner: ApoE2 may be neuroprotective, whereas ApoE4 may be neurodestructive (Kerr and Krauss 1998). ApoE4 is associated with an increased risk of Alzheimer´s disease (Corder et al. 1993, Saunders et al. 1993, Raber et al. 2004, Kim et al. 2009) and attentional and memory impairments in normal controls (Bondi et al. 1995, Berr et al. 1996), even after excluding subjects with mild cognitive impairment or dementia (Caselli et al. 2009).

Several studies have suggested that the ApoE genotype is associated with the outcome after TBI. Associations of ApoE with outcomes after traumatic brain injury (TBI) may be mediated through isoform-dependent modulation of amyloid-β and tau accumulation, mitochondrial functions, or neuroinflammatory responses (Verghese et al. 2011). In the acute phase, the TBI subjects with ApoE4 have shown prolonged unconsciousness (Friedman et al. 1999, Crawford et al. 2002) and lower scores on the Glasgow Coma Scale (GCS) (Ponsford et al. 2007a). In a short-term prospective follow-up study after mild TBI (Liberman et al. 2002), significant associations were found at three weeks after the injury between the presence of ApoE4 and the psychomotor information-processing speed. At

six weeks, no significant associations were any longer found. ApoE4+ indiviuduals with mild TBI showed a decrease in attention and memory performance compared to their pre-injury level, although their performance did not differ from controls or from ApoE4- subjects after mild TBI (Sundstrom 2000). One study on subjects with mild-to- moderate TBI did not find significant associations between the ApoE4 status and cognitive outcome (Chamelian et al. 2004). In a study with more severe TBIs (Ariza et al. 2006) six to nine months after the injury, the group with ApoE4 was weaker in verbal learning, attention, and motor speed. The authors considered that this meant the individuals with ApoE4 had difficulties in tasks that are related to the frontal and temporal lobe and the integrity of the white matter. A two-year follow-up study showed that those with the ApoE4 allele had a slower recovery rate than those without, as assessed with the Glasgow Outcome Scale (GOS), although no differences were found between the groups at individual time points (Alexander et al. 2007).

The few very long-term follow-up studies of individuals with TBI have shown mixed results concerning ApoE4 and cognitive outcome. A study of 396 individuals with severe TBI did not find any significant relationship between ApoE4 and cognitive outcome 18 years after TBI (Millar et al. 2003). In our earlier study, there was a difference in general cognitive level between the individuals with ApoE4+ and ApoE4-, but after the individuals who developed dementia were excluded from the analyses, no significant differences were any longer found (Isoniemi et al. 2006).

Consequently, there are still many open questions and much controversy regarding the ApoE4 status of individuals with TBI and cognitive outcome. If the presence of ApoE4 influences white matter integrity, as suggested, it is important to consider cognitive functions more broadly, without restricting them to episodic memory functions or general cognitive level, especially in long-term follow-up studies. It is possible that all cognitive processes are not similarly affected, or that the role of genetic factors may vary at different time points after TBI.

2.4 Late mortality after TBI and risk factors for reduced survival after TBI

Clinical experience seldom provides the information concerning late mortality or survival time of the individuals with TBI. However, knowledge about the survival time and risk factors for reduced survival are important for several reasons. This knowledge helps in planning interventions and care of the individuals with TBI. It is also important in terms of assessing cost allocation for life-time after TBI. Also families of individuals with TBI

often ask about residual risk factors for the injured individuals. Adequate knowledge of the biostatistical terminology and concepts, along with the literature on the topic, helps the clinician to provide more accurate estimates of survival, and this knowledge may help to prevent risk factors for reduced survival.

2.4.1 Central concepts, terminology, and methods

Survival time is the time period that a given subject of a study population lives. *Life expectancy* is a population-based statistic referring to the mean time that persons within a defined group will survive. *Median survival time,* on the other hand, refers to the time at which one can state that 50% of a large defined population will still be alive. *Life tables* are standard tables summarizing mortality information about a group. Life tables provide specific mortality rate information, that is, they provide life expectancy data at every age. *Exposure time* refers to the number of person-years lived by all the members of a given study population during the duration of the study. *Mortality rate* is the number of deaths in the study population divided by the number of person-years and exposure time. *Mortality probability* is the chance of dying within a given period and expressed numerically as between 0 and 1. *Relative risk (RR)* of mortality is the ratio of the mortality rate in the study population to the mortality rate in the reference population. In the literature the RR is often referred to as the *mortality ratio (MR). Standardized mortality ratio (SMR)* is the ratio of the observed number of deaths in the study population to the expected number.

2.4.2 Studies on late mortality after TBI

2.4.2.1 The initial mortality of individuals with TBI in Finland

The initial mortality and the high-risk mortality caused by TBI are well known. However, the initial mortality incidence rate may vary between countries. A recent study found that the mortality rate in Finland is twice as high as in other Nordic countries (Sundstrøm et al. 2007). The reason for this high incidence rate is unclear. During the study period, the average alcohol consumption did not fully explain the differences, but the authors thought that the “low frequency and high quantity” drinking habit in Finland is a well known risk factor for fatal injuries. Furthermore, the association of accidents with alcohol is more pronounced in Finland than in other Nordic countries. The high frequency of intentional self-harm in Finland could be another explanatory factor for the result.

2.4.2.2 Long-term mortality studies of individuals with TBI

Whereas many outcomes after TBI have been studied earlier, the late mortality of individuals with TBI has been largely neglected. In Finland, no such studies have been conducted. Most of the studies done elsewhere show an increased late mortality risk for individuals with TBI (Shavelle et al. 2001, Teasdale et al. 2001, Harrison-Felix et al. 2004, Ratcliff et al. 2005, Selassie et al. 2005, Pickelsimer et al. 2006, McMillan et al. 2007, Baguley et al. 2008, Cameron et al. 2008, Harrison-Felix et al. 2009, Ventura et al. 2010). Although it is not surprising that individuals with moderate-to-severe TBIs would have a higher mortality rate than the general population, even individuals with mild TBIs have been found to have a small but statistically significant reduction in long-term survival (Brown et al. 2004).

In a cohort study, 2178 individuals with TBI were followed from 17 days to 12.8 years (Harrison-Felix et al. 2009). Of the group studied, 37 % had severe TBI. These researchers estimated an average reduction in life expectancy of seven years. The SMR was 2.00 (95% CI, 1.69-2.31) indicating that individuals with TBI were two times more likely to die than individuals of comparative age, gender and race from the general population. The SMR for individuals with TBI who survived past their one-year post-injury anniversary was 1.95. A retrospective cohort study up to 24 years post-injury also found a twofold increased risk of mortality compared to the general population (Ratcliff et al. 2005). In a prospective follow-up study, hospital-admitted individuals were followed up for seven years (McMillan et al. 2007). Risk of death was noted to be 23 times higher in months 1-2, three times higher in months 3-12, and two times higher in months 13-84 post-injury. Compared with the general population, the death rate after admission to hospital with TBI remained high for at least seven years, and was particularly high for those under age 55.

A study of functionally dependent adults following TBI investigated mortality trends by analyzing data from 966 consecutive admissions to a specialized TBI rehabilitation service (Baguley et al. 2008). Details for 69 of those subjects who were functionally dependent at rehabilitation discharge, were cross-referenced against the state government death register. The observed mortality rate was compared to an equivalent population sample derived from Australian life tables. Twenty-five subjects or 36% were deceased at an average of 10.5 years post-injury. The observed numbers of deaths far exceeded the expected population figure for the same period (1989-2007), yielding a SMR of 13.2. The mortality trend suggested a bimodal distribution with more deaths in the first five years post-injury followed by no further deaths until nine years post-injury.

A population-based study with a matched cohort group examined mortality outcomes for people with TBI (Cameron et al. 2008). The group consisted of 1290 individuals aged 18-64 years. Investigators found that the majority of the deaths (47.2%) occurred in the first 60 days, the adjusted 10-year mortality remained elevated (mortality rate ratio, MRR= 1.4, 95% CI=1.02-2.15). The study found no significantly increased risk in long-term mortality for people who sustained mild, moderate, or moderately severe TBI. Persons with severe TBI were 9.9 times more likely to die than their non-injured counterparts, and those who survived the first 60 days following the injury continued to have a significant risk of mortality during the remaining years of follow-up (adjusted MRR=4.16, 95% CI=1.96-8.84).

2.4.2.3 Causes of death and factors related to survival after TBI

The primary cause of death is the brain damage itself. One large study found that 78% of the deaths were due to injury to the brain stem, brain edema, or brain compression (Sekulovic and Ceramilac 1979). There are studies that have explored the causes of death for a longer time after TBI, although the term "longer time" varies among the studies. It can mean the patients already released from a hospital (Baguley et al. 2000) or one year or longer after injury (Shavelle et al. 2001). Actually, very little data are available beyond one-year post-injury relevant for answering the question of long-term survival patterns or reasons for reduced survival (Zasler 2009).

One large follow-up study of individuals with TBI ranging from 17 days to 12.8 years post-injury (N=2178) found that older age, unemployment at the time of injury, and greater functional disability at rehabilitation discharge remained the most significant risk factors for shorter life expectancy (Harrison-Felix et al. 2004). Another retrospective cohort study showed that pre-injury characteristics such as alcohol abuse and risk-taking behavior were among the strongest predictors of shorter life expectancy, along with the level of functional disability (Ratcliff et al. 2005). A large study of 2140 subjects compared the causes of death between individuals with TBI who survived for at least one year post-injury and the US population mortality rates for 1994 (Harrison-Felix et al. 2006). The follow-up was to 3.1 years post-injury. It was found that individuals with TBI were 37 times more likely to die of seizures, 12 times more likely to die of septicemia, four times more likely to die of pneumonia, and three times more likely to die of other respiratory conditions excluding pneumonia, digestive conditions, and all external causes of injury including poisoning than were individuals that were age-, gender- and race-matched in the

general population. A prospective follow-up study of 767 individuals with TBI (McMillan and Teasdale 2007) showed that mortality during the first year was associated with greater severity of TBI. Pre-injury medical history was associated both with earlier and later deaths, but risk of death remained higher than in the general population also in those with no such history. Later deaths were often associated with suboptimal life-style factors post-injury.

On the whole, the literature is not entirely consistent on which causes of death are reasons for the elevated mortality seen in individuals with more severe injuries. Epilepsy (Shavelle et al. 2001, Ventura et al. 2010), suicide (Teasdale and Engberg 2001), respiratory infections (Shavelle et al. 2001) or diseases of the circulatory system (Shavelle et al. 2001) incidence rates have been elevated among causes of death among individuals with TBI. One very recent study found higher mortality caused by non-seizure neurological disorders and mental/behavioral disorders, but the study did not allow for inferences about causality (Ventura et al. 2010).

Other factors related to long-term survival have been suggested. For individuals with TBI as well as in the general population, age is obviously a determinant of life-expectancy. In the general population, the mortality of males at most ages is higher than that of females and a similar sex-difference has also been found in persons with TBI (Harrison-Felix et al. 2009). Mobility and feeding ability have been documented to be related to long-term survival (Strauss et al. 1998).

3. AIMS OF THE STUDY

The general aim of this thesis was to describe the long-term cognitive course after TBI, and how the cognitive functions after TBI are associated with specific medical factors and reduced survival.

The specific aims of the study were:

I. To describe cognitive change during a 30-year follow-up, and to find factors associated with this change.

II. To evaluate the associations between cognitive functions and MRI findings 30 years after TBI.

III. To compare attentional profiles of TBI subjects with a concomitant mood disorder (depressive symptoms/major depression) to those of patients without a mood disorder, and also to those of healthy controls.

IV. To evaluate the associations between ApoE ε4 and cognitive functions during a 30-year follow-up after TBI.

V. To study late mortality, and to find risk factors for reduced survival after TBI.

4. MATERIAL AND METHODS

4.1 Subjects

4.1.1 Subjects with TBI

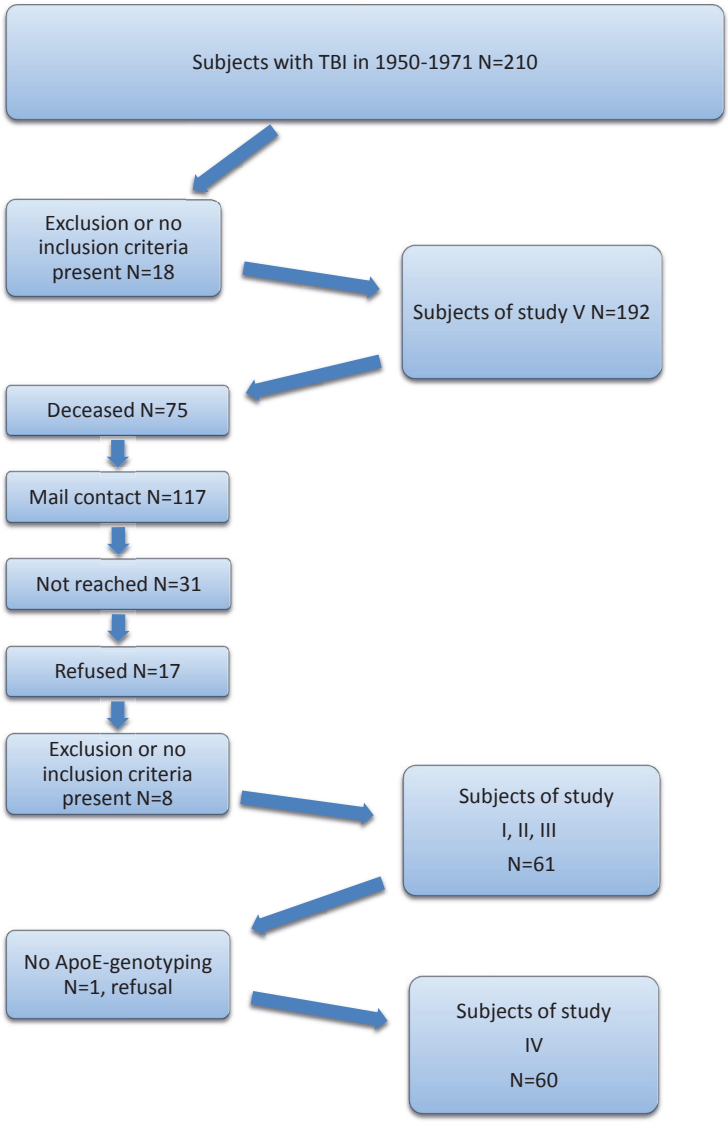

Figure 2. Formation of the study groups

The representativeness of the study group for studies I, II, and III (n=61) vs. the original group was evaluated by restricting the representation analyses to the same age range as in the study group (age at TBI <53 years). The study group was compared with those who were not reached (refused or not reached, n=44), were deceased (n=52) and with those who failed to fulfill the study criteria (n=23). We investigated the subjects in the study group for

This study was a part of a more extensive research project coordinated by the Department of Neurology of Turku University Hospital. The original sample included 210 subjects who had suffered TBI between the years 1950 and 1971 and who had been referred for neurological and neuropsychological evaluation at the Turku University Central Hospital. The reason for the referral was either a recent injury or significant disability after an earlier injury. The neuropsychological evaluations at baseline were carried out in all the referred subjects by the same qualified neuropsychologist (RP) during the years 1966 - 1972.

Inclusion criteria in the present study were: 1) a blunt injury severe enough to cause TBI with neurological symptoms and signs lasting at least one week after the injury (including headache and nausea); 2) at least one of the following: loss of consciousness for at least one minute (eye-witnessed), post-traumatic amnesia (PTA) for at least 30 minutes; neurological symptoms and signs of brain injury during the three days after the trauma (excluding mere headache and nausea), or neuroimaging findings suggesting TBI (e.g. skull fracture, intracerebral hemorrhage). With these inclusion criteria we wanted to exclude trivial TBIs where the likelihood of long-term consequences is minimal. Exclusion criteria were: 1) any brain disease prior to TBI; 2) clinical symptoms of a nontraumatic brain disease developed after TBI (excluding degenerative dementia); 3) medical records not available.

Information about the TBI was evaluated retrospectively from medical records by the neurologist (OT) and, where possible, with a personal interview. All subjects had suffered a closed head injury. The severity of TBI was classified according to the duration of LOC and/or PTA, as originally described by Russell and Smith (1961) : <1 h = mild; 1 – 24 h = moderate; 1 - 7 days = severe and >7 days = very severe.

In the original sample of 210 subjects, 12 subjects did not meet the inclusion criteria listed above, showing only signs of a very mild TBI. Exclusions were made due to an earlier brain disease (n = 1), a nontraumatic brain disease after TBI (n = 2), and missing medical records (n = 3). Thus, the final sample for study V included 192 subjects. Survival of the subjects was followed up to 31.12.1996, i.e. between 24 and 30 years from the neuropsychological assessment. By the end of the follow-up, 75 subjects had died. The remaining 117 patients were contacted by mail, and 86 of them responded. Eight subjects failed to meet the study criteria and 17 subjects refused to participate in the study. Thus, the remaining 61 subjects formed the study group for studies I, II, and III. One subject refused ApoE-genotyping, thus 60 subjects were included in study IV.

A flow chart of the selection procedure of the subjects is presented in Figure 2.

The representativeness of the study group for studies I, II, and III (n=61) vs. the original group was evaluated by restricting the representation analyses to the same age range as in the study group (age at TBI <53 years). The study group was compared with those who were not reached (refused or not reached, n=44), were deceased (n=52) and with those who failed to fulfill the study criteria (n=23). We investigated the subjects in the study group for the following variables: age, gender, education, severity of TBI, and score on the Mild Deterioration Battery in the original examination (describes general cognitive decline; see the methods section) at the time of injury. The study group did not differ from the original group according to gender, severity of TBI, or general cognitive level. However, the study group consisted of younger patients than the deceased and those who did not meet the study criteria ($p<0.001$), and the study group was also better educated than the patients who had died ($p<0.001$). Table 1 shows the characteristics of the patient material.

Table 1. Characteristics of the patient material

Variable	Study I,II,III n=61 Mean (SD)	Study IV n=60 Mean (SD)	Study V n=192 Mean (SD)
Age at injury, y	29.4 (10.8)	29.3 (11.0)	37.0 (13.8)
Age at original assessment, y	32.4 (10.2)	31.8 (10.1)	39.0 (13.2)
Age at follow-up assessment, y	60.1 (10.6)	60.3 (10.5)	-
Time from injury, y	31.0 (3.6)	31.0 (3.6)	2.0 (3.0)
Education, y	10.0 (3.3)	10.0 (3.3)	8.5 (2.1)
Gender, m/f (%)	67.2/32.8	67.2/32.8	65.0/35.2
Severity of TBI (%)			
Mild/Moderate	47.6	46.7	69.6
Severe/very severe	52.4	53.3	30.4
Cause of TBI (%)			
Traffic accidents	62.3	61.7	52.9
Falls	23.0	23.3	28.3
Assaults	3.3	3.3	2.6
Others	11.5	11.7	16.2

4.1.2 Control subjects

We recruited 31 healthy volunteers through a local newspaper advertisement as a control group to evaluate cognitive impairment in the follow-up assessment (Studies I, III). TBI, neurological, psychiatric, and other severe diseases were exclusion criteria. The control group was similar to the study group in regard to age and education. There were more women in the control group than in the study group, but the difference was not significant.

4.2 Methods

4.2.1 Cognitive and neuropsychological methods

The cognitive methods were partly the same both in the original assessment (R.P.) and in the follow-up assessment (L.H.). The methods for the original publications are presented in Table 2.

4.2.1.1 Methods for episodic memory and verbal learning

The Wechsler Memory Scale (WMS) associative learning was used (Wechsler 1945). The subject was asked to listen to 10 word pairs and then remember the correct paired associate with the first word presented orally. This was repeated twice more (maximum correct score 30). After one hour the subject was asked to remember the correct paired associate when each word was presented orally (delayed recall).

The 20 object memory test (Portin et al. 1995). The object memory test consists of an array of 20 common objects placed on a 20 x 30 cm tray. After the instructions, the tray was presented, and the subject had to name all the objects. The total encoding time was 75 seconds, after which the tray was removed and the recall was asked for immediately.

The Benton Visual Retention Test (BVRT version C) (Benton 1963). The BVRT consists of ten sets of figures, shown one set at a time for ten seconds. After the study phase, the set was removed and the subject had to draw the items on a piece of paper.

A memory questionnaire (Sunderland et al. 1983) was used to evaluate subjective memory problems in everyday life (study II). In the questionnaire, the subject is asked to evaluate memory in everyday situations (e.g. remembering names, faces, places etc.) on a five point scale (maximum score of 136).

4.2.1.2 Methods for attention, information-processing speed, and executive functions

The Trail-making test (Lezak 1983)**.** Part A requires, after a brief practice, the connection by pencil lines of 20 encircled numbers (1-20) positioned randomly on an A4-sized page. Part B requires the participant to alternate between numbers and letters (e.g. 1-A-2-B-3-C…). The scoring includes the total time the participant takes to complete each part, including the time for the correction of mistakes.

The Modified Wisconsin Card Sorting test (MWCST) (Nelson 1976). The MWCST consists of four stimulus cards each of which is unique in terms of its color, shape, and number of items. Twenty-four response cards shared one attribute with each of the stimulus cards. The subject was asked to sort the response cards under the stimulus cards according to certain rules. The examiner does not tell what the rule is, but after every response the examiner indicates whether the move was right or wrong. The total number of errors and perseverative errors was calculated.

The Verbal fluency tests (Lezak 1983)**.** In the first test, the participants were asked to produce as many words as they could that begin with a given letter (s) within a 60-second period. In the second test, the subject was asked to produce as many names of animals as possible within a 60-second period.

The CogniSpeed software (Revonsuo and Portin 1995): Simple reaction time (SRT), two choice reaction time (2-CRT), ten-choice reaction time (10-CRT), subtraction test (ST), visual recognition thresholds, and vigilance (VT). In the SRT test, the subject had to press the '0' key every time the target '0' appeared on the screen with random delay ranging from 1 to 4 seconds. In the 2-CRT test, the numbers 0 and 1, and in the 10-CRT, the numbers 0 - 9 appear in the middle of the screen, and the subject had to press the corresponding number (number pad keys on the right-hand side on a standard IBM-compatible PC keyboard). The ST test is identical to the 10-CRT test, but the instruction given to the subject is different: the number appearing on the screen has to be subtracted from nine, and the key corresponding to the remainder pressed. The measure for the subtraction time was calculated as the difference in reaction times between the ST and the 10-CRT, which had similar perceptual and motor requirements. Automatic cognitive processing was studied in a task of recognition thresholds with 10 targets (4 numbers and 6 letters). The letter 'X' was shown in the middle of the screen and, after an auditory signal, 'X' was replaced by a target item. The presentation time was started from 14 ms and was increased by 14-ms steps, until the target was recognized. The time required was recorded separately for all

items. In the vigilance test, two target letters (Y, L) appear on the screen with a probability of 20 % of all 600 letters presented during 15 minutes, and the subject is asked to press the spacebar immediately the target letter appears.

4.2.1.3 Methods for verbal and visuomotor performance

The Wechsler Adult Intelligence Scale (WAIS) (Wechsler 1955): Arithmetic, Similarities, Digit Span, Digit Symbol and Block Design subtests. The test of Similarities puts demands on conceptual knowledge and semantic memory. The subject had to express in which way two verbally presented items were alike. In the Digits Span, attention and working memory are required. The digit Symbol is a test of visuomotor speed and the Block Design is a test of visuoconstructive skill.

4.2.1.4 Methods for general cognitive level: the MMSE and the Mild Deterioration Battery

The general cognitive level of the subjects was screened by the MMSE (Folstein et al. 1975), and further, with the Mild Deterioration Battery (MDB) (Portin 2000, Kujala et al. 1995).

The MDB consists of two verbal (Similarities, Digit Span) and two nonverbal subtests (Digit Symbol, Block Design) from the WAIS (Wechsler 1955), as well as four other tests: the Object Memory test (naming time and immediate recall of 20 objects), immediate recall of 30 Paired Word Associates (PWA) (Portin and Rinne 1980), and BVRT (form C, Benton 1963). These eight tests served as separate measures for verbal, visuomotor and episodic memory performances. Additionally, the delayed recall of both 20 objects and 30 PWA was requested after one hour. The visual episodic memory was evaluated with the BVRT form C, verbal-visual episodic memory with the Object Memory test, and verbal episodic memory with the 30 PWA. The MDB is a more sensitive measure than the MMSE in differentiating neurological patients with an incipient cognitive decline from the patients without cognitive impairments (Kujala et al. 1996). The patients received one deterioration point if they performed at least 1.5 standard deviations below the mean in any of the MDB tests when compared to our earlier Finnish norms (Portin and Rinne, 1980); two points, if below 2 SD; and three points, if below 3 SD. Thus, the maximum deterioration score was 24 points. The results were re-scored as described earlier (Kujala et al. 1994).

4.2.1.5 Methods for depressive symptoms and major depression (Study III)

The presence of depressive symptoms was evaluated with the short form of the Beck depression scale (Beck and Beck 1972); the cut-off score of five points was used to separate TBI with and without depressive symptoms. The presence of major depression was evaluated with Schedules for Clinical Assessment in Neuropsychiatry (version 2.1) (Wing et al. 1990) (SCAN) as described earlier (Koponen et al. 2002).

Table 2. Neuropsychological methods. The roman numerals refer to the original publications.

Verbal and visuomotor tests:
WAIS:Similarities (I,IV)
Digit Span (I,IV)
Digit Symbol (I,IV)
Block Design (I,IV)
Naming of 20 objects (I,IV)
Episodic Memory
Recall of 20 objects, immediate and delayed recall (I-II, IV)
Benton visual retention test (I-II, IV)
WMS: Recall of 30 paired word associates (I-II, IV)
Memory Questionnaire (II)
Attention, information-processing speed and executive functions
The trail-making test (II-III)
The modified Wisconsin card sorting test (II-III)
The verbal fluency tests (II-III)
The CogniSpeed software (III-IV)
Automatic processing:
Recognition of numbers and letters
Controlled processing and attention:
Simple RT
2-choice RT
10-choice RT
Subtraction time
Vigilance
General cognitive decline
The Mild Deterioration Battery (I,IV,V)
MMSE (I,II,III)
Depressive symptoms/major depression
The Beck depression scale (I,II,III)
SCAN (III)

4.2.2 Magnetic resonance imaging (MRI) (Studies I,II)

The MRI scans were acquired with a 1.5 T Siemens Magnetom system using a standard head coil. In addition to the routine T2-weighted axial sequence sagittal, a three-dimensional MPR (magnetization prepared rapid gradient echo; TR 10, TE 4, flip angle 10°, matrix 192 x 256, contiguous 1.5 mm slices, 1 acquisition) sequence was obtained in all cases. For volume measurements, oblique coronal 3-mm-thick slices oriented perpendicularly to its long axis of the hippocampus (hippocampal volumes) and axial 3-mm-thick slices (volumes of lateral ventricles) were reconstructed. Volume measurements were performed on a standard work console by manually outlining the right and left hippocampus and the lateral ventricles. The areas of successive slices were summed and multiplied by the slice thickness.

Hippocampal volumes were measured according to a previously described report (MacKenzie et al. 2002). The hippocampus included the Ammon´s horn, the gyrus dentatus, the subiculum and the uncus ventral to the caudal amygdala; the slice in which the fornices were visible for their full length determined the posterior end of the hippocampus. The intra-cranial coronal area was measured at the level of the anterior commissure; this area was used to normalize the volumes in relation to head size. The presence of contusions on MRI images, as well as volumetric measurements, were assessed by an experienced neuroradiologist.

4.2.3 The alcoholism screening

Abuse of alcohol was controlled by the Short Michigan Alcoholism Screening Test (SMAST) in study I. This test includes 13 questions about a subject's involvement with alcohol during the past 12 months (Appendix).

4.2.4 ApoE genotyping (Study IV)

To perform the ApoE-genotyping assays, 3 mL of EDTA anticoagulated blood was collected from each subject. Genomic DNA was extracted from fresh or frozen whole blood using either the Amersham Nucleon DNA-extraction kit (GE Healthcare, Buckinghamshire, UK) or a modified salting-out procedure (Donohoe et al. 2000). The quality and quantity of DNA were then measured by spectrophotometry, and samples were diluted to a final concentration of 20 mg/L. The determination of the six major genotypes of ApoE

was performed using a multiplex amplification refractory mutation system polymerase chain reaction (ARMS-PCR), as previously described (Donohoe et al. 1999). Each PCR run included negative controls, as well as three to five samples of known ApoE genotypes as positive controls. One subject refused to undergo the ApoE-genotyping, and thus the final study group consisted of 60 subjects. Distribution of ApoE genotypes was as follows: 4/4 (n = 5), 3/4 (n = 13), 2/4 (n = 1), 3/3 (n = 31), 2/3 (n = 10), 2/2 (n = 0). We decided to further group the subjects into those with the ApoE4 allele (n = 19, 31%), and those without the ApoE4 allele (n = 41, 69%).

4.2.5 Assessment of survival (Study V)

Survival of the subjects was followed up to 31.12.1996, i.e. between 24 and 30 years from the original neuropsychological assessment. Survival and the dates of death were derived from the national registry; there were no lost cases. The causes of death were collected from the Statistics Finland register. There were three subjects with missing records. The mortality was also compared to that of the general population; these comparison data were also derived from Statistics Finland.

4.2.6 Statistical analyses

Data of subjects with TBI and normal controls were characterized using means and standard deviations (SD) or medians. Furthermore, the range of values was presented. Categorical variables were characterized using frequencies and percentages. The normality of continuous variables was tested with the Kolmogorov-Smirnov test for normality. To test differences between groups, either the Mann-Whitney u-test or the Student t test was used. The Chi Square test was applied to the categorical variables, as was the Fisher exact test when needed. A two-sided p-value of less than 0.05 was considered significant in all the analyses.

The paired sample t-test was used to compare the cognitive performances between the original and follow-up examination (Studies I, IV). In Study I, multiple regression analyses were used to examine the association between change in the MDB score (response variable) and other variables (explanatory variable). To analyze the interaction between two explanatory variables on the response variable, a general linear model/ univariate analysis was used.

In Study II, Multiple linear regression analyses were used to explore the associations between neuropsychological measures and other variables, such as MRI measures.

The analyses were done for each cognitive variable as response (enter procedure). The regression analyses were adjusted by age, education, and gender to control for the effect of these background variables. R^2 was used to describe the statistical model of the regression analyses.

In Study III, analysis of variance (ANCOVA) was used with the group as a between-subject factor, with three categories (depressive patients, non-depressive patients and controls) and post-hoc pairwise comparisons were conducted. In Study IV, ANCOVA was used to compare cognitive performance of the subjects between the ApoE genotype groups (ApoE4- and ApoE4+). These analyses were adjusted with age, gender, and education. In these analyses, Bonferroni post-hoc tests were applied to control for the effect of multiple comparisons. In Study III, the association between the Beck score and cognitive variables was also explored with the partial correlation technique; in these analyses, age was used as a covariate.

In Study V, risk factors for reduced survival of subjects with TBI were studied using the Kaplan-Meier technique and Cox's regression analysis. All explanatory variables were analyzed separately, and the stepwise method was used to define the final multivariate model from the variables that were statistically significant in univariate analysis. The results were quantified by calculating hazard ratios (HR) with 95% confidence intervals (95% CIs). The mortality of the subjects was compared to that of the general population of Finland using the standardized mortality ratio (SMR) which is the ratio between the number of observed deaths and the number of expected deaths. The number of expected deaths (by age, gender and year) was calculated by multiplying the number of persons at risk by the mortality rate of the Finnish population. Poisson regression analysis was used to estimate SMRs with 95% CIs. SMRs were estimated by the follow-up period, gender and age (age defined for persons at risk for each period). The vocational outcome of the subjects was considered as an ordinal variable and cumulative logistic regression analysis was used in the analyses. Probabilities of belonging to lower ordered values of the variable (more impact on vocational outcome) were modeled, and therefore the concept of poor vocational outcome is used in the results instead of specific classes of outcome variable. First, all explanatory variables were analyzed separately and then the stepwise method was used to define the final multivariate model from the variables that were statistically significant in univariate analysis. To justify the use of cumulative logistic regression analysis, the Score test was applied to test the assumption of proportional odds. The results of analyses were quantified by calculating cumulative odds ratios (ORs) with 95% CIs.

Statistical computations were performed using SAS System for Windows, Version 9.2 (SAS Institute Inc. Cary, USA).

4.2.7 Ethical considerations

After a complete description of the study to the subjects, written informed consent was obtained. The protocol was approved by the Conjoint Ethics Committee of Turku University and Turku University Hospital.

5. RESULTS

5.1 Longitudinal cognitive changes after TBI (I)

A decline in performance between the original and the follow-up assessment (I: Table 2) was seen in the verbal (the arithmetic subtest of WAIS, $p < 0.001$) and the visuomotor domain (the Block Design, $p < 0.001$), and in the immediate recall of the episodic memory tests ($p < 0.001$ to $p = 0.027$). Contrary to this, the raw score of the Similarities improved during the follow-up time ($p < 0.001$). In the original assessment, the subjects had a mean MDB score of 2.5, which is classified as mild cognitive impairment. In the follow-up assessment, the mean score was significantly higher (4.7; $p = 0.002$), describing a moderate cognitive impairment. However, all patients did not contribute to this change, as 13 (21.3%) patients remained at the same level as in the original examination, 14 (23%) improved, and 34 (55.7%) showed decline in their MDB scores. These three groups did not differ from each other in their depression score, severity of TBI, or gender. However, those who improved were significantly younger than those who remained at the same level.

The rise in the MDB score was associated with male gender ($p = 0.015$) and with higher age at injury ($p = 0.010$). No significant association was found between education, depression, severity of TBI, abuse of alcohol, later TBIs, ischemic findings in MRI, or time since injury at the original assessment. There was no significant difference in the MDB scores (or in any other cognitive test) between the sexes at the original assessment, but the men's MDB score had doubled in the follow-up assessment ($p < 0.001$), whereas the women remained at the same level as in the original examination (I: Figure).

When the patients were divided into two groups according to the severity of injury (mild-to-moderate vs severe-to-very severe), no differences in cognitive performance were found either in the original or in the follow-up assessment. However, in the longitudinal analyses, the more severe group showed a decline in the immediate recall of the WMS associative learning (mean -2.6 points; $p = 0.010$), whereas the milder group did not. On the other hand, the more severe group improved in the Similarities raw score (mean +2.2 points; $p = 0.005$), whereas the change in the milder group did not reach significance. An improvement in the raw score of Digit Span/Backwards was seen in the milder group (+0.6 point, $p = 0.023$) but not in the more severe group.

The subjects with TBI performed more poorly than the control group on all cognitive tests ($p < 0.001$ to $p = 0.026$). (I: Table 2).

5.2 Cognitive functions in relation to MRI findings 30 years after TBI (II)

Both left and right hippocampal volumes were generally associated with memory and executive functions: smaller volumes were associated with reduced cognitive performance, although only few tests reached significance. The volume of the left hippocampus was significantly associated with the WMS associative learning test (immediate recall), the errors in the MWCST and with the Memory Questionnaire. The volume of the right hippocampus was significantly associated with the 20 objects memory test (delayed recall), the WMS associative learning test (immediate recall), and the preservative errors on the MWCST. (II: Table 3).

The volume of the lateral ventricle was associated with the 20 objects memory test (delayed recall), the Benton Visual Retention Test, the errors and the perseverative errors on the MWCST, and with subjective reports on the Memory Questionnaire. As with the hippocampal volumes, signs of tissue loss (larger ventricular volume) tended to associate with low cognitive performance. (II: Table 3).

A local contusion finding (either cortical or subcortical) on the MRI was associated only with lower performance on the WMS associative learning test, on both immediate and delayed recall (II: Table 3).

5.3 Attention and depressive symptoms in chronic phase after TBI (III)

The TBI group with major depression (n=6), as assessed with the SCAN, did not differ from the rest of the patients with TBI in any cognitive methods used. The Beck score, however, was higher in the group with major depression compared with the rest of the TBI patients ($p = 0.047$)

The cognitive performance of subjects with depressive symptoms (Beck score ≥ 5, $n = 32$), patients without symptoms (Beck score < 5, n=29), and controls (n=31) were compared with analysis of covariance (III: Table 3). The TBI subjects with depressive symptoms were slower on the SRT ($F=10.5$, $p < 0.001$, post-hoc $p = 0.002$) and performed more poorly on the VT, having a lower total hit rate (4.1, $p = 0.003$, post hoc $p = 0.045$) than the patients without depressive symptoms. Also the RT of letters differed between the groups, the depressive patients being slower ($F=8.2$, $p < 0.001$, post-hoc $p = 0.018$). No other cognitive differences were found between TBI subjects with and without depressive symptoms.

The non-depressive TBI patients performed generally more poorly on the attention and speed-related tests than the control group (III: Table 3). Significant differences were

found in verbal working memory (ST, F =7.1, p < 0.001, post-hoc p = 0.038), in tests that require cognitive flexibility such as Trail-Making B (F=9.3 p<.001, post hoc p =0.017), total number of errors (F=13.7, p = 0.001, post hoc p=.003), and in categories (F=12 p <.001, post hoc p = 0.004) on the MWCST, and in the word fluency tests (F=13.4 p <0.001, post hoc p =0.010 for animals, F=12.0 p <.001, post hoc p = 0.001 for s-alphabet). There was also a difference in the automatic information processing, since the non-depressive TBI patients were slower than controls in the visual recognition of numbers (F=9.0, p < 0.001, post hoc p = .036).

5.4 Apolipoprotein E ε4 and cognitive functions after TBI (IV)

5.4.1 Differences in cognitive performance between ApoE4+ and ApoE4- groups in the original assessment and in the follow-up assessment

Verbal and visuomotor performance on the WAIS was generally lower in most of the tests in the ApoE4+ group than in the ApoE4- group, but no significant differences were found in the original or in the follow-up assessment (IV: Table 2). In a longitudinal analysis (data not shown, analyzed with the paired t-test), performance on the Similarities subtest of the WAIS improved in the ApoE4- group (p< .001; the original vs. the follow-up assessment) during the follow-up, while no improvement was seen in the ApoE4+ group (p=0.770; the original vs. the follow-up assessment): the difference between the groups was significant (p<0.039, difference in the group means during the follow-up, IV: Table 2).

Subjects with ApoE4 had more difficulties than subjects without this allele in verbal learning in the original assessment (p=0.018) but no differences in verbal learning were found in the follow-up assessment (p=0.593; IV: Table 2). In the follow-up assessment, the visual memory performance was weaker (p=0.027), and the naming time of objects was lower (p=0.020) in the ApoE4+ group than in the ApoE4- group (Table 2). There was a decline (paired t-test, data not shown) in verbal learning during the follow-up in the ApoE4- group (p=.005; the original vs. the follow-up assessment), while no decline took place in the ApoE4+ group (p=0.653; the original vs. the follow-up assessment): the difference between the groups was significant (p< 0.047, difference in the group means during the follow-up, Table 2). Otherwise, no differences were found between the groups.

The overall cognitive impairment (MDB score) was weaker in the ApoE4+ group in the follow-up assessment (p=0.007), while no difference was seen in the first assessment (IV: Table 2).

5.4.2 Differences in cognitive performances between ApoE4+ and ApoE4- groups in the CogniSpeed tasks in the follow-up assessment

No differences were found in the simple or two-choice reaction time in the follow-up assessment, but the subjects with ApoE4+ were slower in the ten-choice reaction time tasks (0.033) and in the subtraction tests (p=0.011) than the ApoE4- group (IV: Table 3).

The ApoE4+ group was slower compared with the ApoE4– group in the subtraction time which describes pure cognitive processing speed in verbal working memory.

The reaction times were no different between the ApoE groups in the Vigilance test. There was a non-significant trend for the ApoE4+ group to make more mistakes and have fewer correct responses during the 15-minute vigilance task.

The automatic processing and visual recognition speeds were no different between the ApoE groups.

5.5 Risk factors for reduced survival after TBI (V)

5.5.1 Risk factors for reduced survival

Fifteen subjects (8 %) died during the first decade, 31 (16 %) during the second decade, and the remaining 29 (15 %) died during the third decade after the injury. Thus, by the end of the follow-up, 75 (39.1 %) subjects had died.

Univariate analysis showed that higher age ($p < 0.001$), presence of other illnesses ($p = 0.0l8$), and the vocational outcome ($p < 0.001$) were associated with reduced survival (V: Table 2). Lower education level was also a risk factor for death, as the patients with the lowest level of education had the highest risk of death. The degree of cognitive impairment was a nearly significant ($p = 0.068$) risk factor for reduced survival during the 30-year follow-up period. During the first 18 years of follow-up, the cognitive level did not seem to have any influence on survival, but later on (during the third decade after the injury) the more cognitively impaired had an increased risk of death compared to those with milder impairment (V: Figure 1). In the multivariate analysis, age ($p < 0.001$) and poor vocational outcome ($p=0.004$) were independent risk factors for death during the follow-up. Other factors studied were non-significant.

Because the vocational outcome was an unexpected and significant risk factor for reduced survival in the multivariate analyses, associations with vocational outcome were further explored**.** Information on retirement events after TBI showed that 42.8 % had re-

tired immediately after TBI, 17.2 % during the following five years, 4.6 % during the following 6 - 14 years (but before normal retirement age), and 8.6 % had continued working longer than 15 years but retired before normal retirement age. Of all subjects, 26.5 % continued up to normal retirement, but 15.5 % at a lower level compared to their original occupation, and thus only 11.0 % had a normal working career up to normal retirement age, or were still in productive working life at the follow-up point of 31.12.1996.

Risk factors for early retirement or lowered ability to work are presented in study V (V: Table 4). Univariate analyses of the explanatory variables showed that higher age ($p = 0.001$) and male gender ($p = 0.020$) were associated with early retirement or reduced working ability, as well as moderate-to-severe TBI ($p < 0.001$) and at least moderate cognitive impairment ($p < 0.001$). Further, the occurrence of later TBIs ($p = 0.034$), post-traumatic epilepsy (PTE; $p = 0.005$) and alcohol abuse ($p = 0.008$) were associated with poor vocational outcome. Subjects with a higher level of education had a lower risk for poor vocational outcome than those with the lowest level of education (OR 0.08, 0.02 to 0.39). The presence of other diseases or earlier TBIs was not associated with vocational outcome. Whether a subject was a student or working at the time of TBI had no effect on the vocational outcome. In multivariate analysis, higher age ($p < 0.020$), severity of TBI ($p < 0.001$), greater cognitive impairment ($p = 0.001$), later TBIs ($p = 0.007$), and abuse of alcohol ($p = 0.014$) were independently associated with early retirement or reduced working ability.

5.5.2 Mortality comparison with the general population

The SMR was slightly higher for the entire TBI group compared with the general population during the whole follow-up period (SMR = 1.25, 95% CI= 0.99-1.57), but this difference was not statistically significant. However, SMR was significantly higher (SMR = 4.50, 2.02 to 10.01) in the younger subjects (age at death <40 years; V: Table 3, Figure 2). The mortality during the second decade of follow-up differed significantly from the expected (SMR = 1.47, 95% CI= 1.06 - 2.05). Male subjects with TBI had higher SMRs compared with the respective population (SMR = 1.34, 95% CI= 1.02 - 1.77), even though the difference in SMRs was not statistically significant between the genders. A closer look at the patients (n=6) who died under the age of 40 years revealed that there were two suicides and one homicide. The other reasons for death were neoplasms (n=2), and one patient died of pneumonia.

6. DISCUSSION

6.1 Material and methods

6.1.1 Subjects

A limitation of this study is that the subjects are selected, since the referral had been made on a clinical basis to the neurological clinic. This means that those who recovered completely were probably never referred. However, the author who originally assessed the subjects with TBI (RP) wanted to meet all the patients with TBI referred to the clinic, no matter whether they complained about neuropsychological problems or not. In those days, focusing on a certain patient group was possible for the clinical neuropsychologist. The characterization of the subjects generally as having "mild cognitive impairment" (I) fits well with the clinical experience of patients with TBI of variable injury severity. Moreover, the concept of unselected subjects of TBI is somewhat ideal, since a vast number of subjects with TBI never seek medical care (Sosin et al 1996, McCrea et al. 2009, Delaney and Frankovich 2005). Fully unselected TBI materials might not be relevant to clinical practice since the majority of patients with mild injury recover without long-term cognitive impairment (Carroll et al. 2004, Belanger et al. 2005, Iverson 2007). Since, in reality, the majority of TBIs are mild, our study group does not represent TBIs in general but the more severe injury continuum (52 % of the patients in the follow-up study had severe/very severe TBIs; Table 1.). Moreover, some of the patients may have had more symptoms than in general because of the clinical referral. These are the reasons why our results may not be generalized to all subjects with TBI.

The representativeness of the study group for studies I, II, and III (n=61) vs. the original group was evaluated by restricting the representation analyses to the same age range as in the study group (age at TBI <53 years; II: Figure 1.). The study group did not differ from the original group according to gender, severity of TBI, or general cognitive level as assessed with the MDB. However, the study group consisted of younger patients than the deceased and those who did not meet the study criteria, and the study group was also better educated than the patients who had died. Based on these evaluations it seems that no serious bias occurred due to attrition of the subjects. Moreover, the seriousness of the attrition problem has been questioned lately (Deeg 2002, Powers and Loxton 2010). A

male majority is typical among subjects with TBI, and this characteristic is present also in all the studies (I-IV: 67.2%, V: 65.0%).

We had a control group of healthy persons for cognitive comparison. This group was age- and education-matched at group level at the follow-up assessment. With this control group we could compare the findings in a cross-sectional way (I, III), but we did not have a control group for the longitudinal comparison (I, IV).This is a major disadvantage, especially in studies I and IV. Without a longitudinal control group we cannot truly differentiate the effects of TBI on cognition from other cognitive influencing factors. To overcome some of this limitation we used injury severity dichotomy for controlling TBI itself (I). On the other hand, earlier studies of longitudinal recovery after TBI face the same shortcoming of a missing control group. Given this truly long-term follow-up time, the claim for this kind of control group may not be reasonably realistic. Moreover, the literature also lacks truly long-term longitudinal studies of cognitive functions in healthy subjects. The fact that we did not conduct MRI in the control subjects can be considered another flaw.

Although the size of the study sample is moderate for a clinical cognitive study, it proved to be small for some of the research questions. This was especially apparent in the subgroup analyses of studies III (the subjects with major depression vs. other subjects with TBI) and IV (different Apolipoprotein-genotype groups). The mortality comparison to the general population had lability due to the small number of patients (V: Table 4, Figure 2) in the different follow-up periods. For this reason the results should be regarded with caution.

At the time of the original assessment and clinical evaluation, neither the Glasgow Coma Scale nor assessment of PTA was in systematic clinical use. The evaluation of trauma severity was based on all data available. The reliability of retrospective evaluation may have been affected by patients´ cognitive ability, missing or inadequate information in the medical records, and a lack of neuroradiological assessment tools at the time. The results on injury severity are to be interpreted with caution.

6.1.2 Cognitive methods

In order to study longitudinal cognitive changes after TBI (I), the methods had to be the same as in the original assessment (RP). Therefore, the same methods were used in the follow-up assessment. These include five tests from the WAIS, the associative learning test of the WMS, the BVRT and the object memory test, and the MDB. The WAIS, WMS

and the BVRT are widely known and they have been intensively studied. Given the cognitive heterogeneity of the material of the subjects with TBI and the long-term follow-time, the aspects of reliability of the tests are of crucial importance. The sensitivity of tests in this kind of study design may not be a priority, since with the increasing sensitivity of the tests, false positive results are likely to occur. The lack of previous long-term longitudinal follow-up studies is another reason why well known and studied methods may give a better picture of the cognitive course than less studied methods.

There proved to be several advantages of using the MDB in studies I, IV and V. It is a global index for cognitive impairment that covered multiple cognitive domains, including episodic memory, verbal, and visuomotor functions. A single cognitive test could have been too narrow an instrument to give a description of global cognitive functioning. Moreover, it is a practical instrument in the multi-factorial analyses of the studies. It is not very time-consuming; it can be administered in an hour. It is also more sensitive in revealing incipient cognitive impairment than shorter methods such as the MMSE (Revonsuo et al. 1993, Kujala et al. 1994, 1997). Although not directly comparable with the clinical evaluation of dementia, there is a strong association between the two assessments for dementia (Koponen et al. 2002). The sensitivity of the MDB may not be the best to evaluate TBI-related symptoms, since many aspects of TBI we nowadays consider crucial are not covered. These include ToM tasks, methods for complex attention and executive functions, and modern cognitive processing-speed methods. However, these methods were not available when the original assessment was conducted. The sensitivity of the MDB may be poor especially in the patients with mild injuries and in the original assessment when the subjects were young. Further, the cut-off score of one deterioration point has been 1.5 SD instead of 1 SD, which would have been more sensitive. We are aware of the fact that we did not have exact information about the pre-injury cognitive functions, other than what we could infer from the pre-injury educational or vocational level. None of the subjects had had a need for special education before TBI. This means that in the majority of the patients their pre-injury cognitive level was within average range. However, we cannot rule out the possibility that some of the subjects may have had pre-injury cognitive weaknesses, especially in specific cognitive domains. This could have been a confounding factor for the results. To overcome some of the pre-injury cognitive effects, we used the number of education years as a covariate in the statistical analyses, whenever possible.

We used some classical cognitive methods in studies II and III to measure the so-called frontal cognitive functions: attention (both focusing and divided attention), executive functions, and cognitive flexibility (the ability to modify one's response in relation

to task demands). The Modified Wisconsin Card Sorting test, the Trail-Making A and B-test, and word fluency tests were used. The problem with these methods is that many other factors than solely frontal anatomical circuits, may be involved. The performance on these tasks may be influenced by general intelligence and education (Vilkki et al. 1994) and it may also be impaired after diffuse brain damage, inefficient integrative functioning, and after damage to many nonfrontal brain regions (Stuss 2007). It should be noted that some aspects of executive functions are not easily detected by cognitive tests. To attain personal life goals may be one of them; no one else can set life goals, either short- or long-term goals, for you. In general, human cognition is more forward-looking, proactive rather than reactive. Importantly, goal-directed behavior disturbances are well known disturbances after TBI (Wood 1990, Goldberg 2001). Furthermore, subjects with TBI often lose their cognitive integrity in their personal life, even when the cognitive performance may be quite accurate in many so-called classical frontal tests. The questionnaires assessing executive functions, and especially the comparison of the subjects' and their relatives/closest informants' answers, could have given a better picture of the executive functions in everyday life. This kind of approach is also used in studying subjects' insight into their cognitive or emotional changes after TBI.

The CogniSpeed© software uses the reaction time paradigm, 'mental chronometry', which focuses on the time course and structure of mental events occurring between the presentation of the stimulus and the execution of the response (Posner 1978). Stuss et al. (1995) have proposed a model of anterior attentional functions, comprising various domains, such as preparing, concentrating, sharing, suppressing, and sustaining attention. These categories have been utilized in CogniSpeed© tasks. Applying subtracting logic (Shoben 1982), differences between complex and simpler tasks of similar perceptual and motor requirements were taken as measures of pure cognitive processing (IV). This test has been shown to be sensitive enough to reveal differences known to be related to aging (Portin 2000). Earlier this method has been used in studies of various patient groups, including patients with Parkinson's disease (Portin et al. 2000, Revonsuo et al. 1993), with MS (Kujala et al. 1994), and with cancer patients (Salminen et al. 2003). It has been sensitive enough in studying effects on sleep deprivation (Alhola P and Polo-Kantola P 2007), and the hormonal effects on cognition (Portin 2000) in healthy subjects. Although the CogniSpeed© has not been used in earlier studies with subjects with TBI, similar computerized methods have been used especially in studies on recovery from sport-related mTBI (Bleiberg et al. 2004, Lovell et al. 2004).

6.1.3 MRI

Although MRI is more sensitive in detecting traumatic lesions in the brain than CT, it is nowadays evident that there is partial resolution of MRI lesions in the chronic stage after TBI. This means reduction of visibility of both cortical contusions and other intraparencymial injuries (Brandstack et al. 2006). Thus a standard MRI may not be sensitive enough to study patient material when injuries occurred 30 years ago (I, III). The use of fluid-attenuated inversion recovery (FLAIR) sequence and diffusion-weighted imaging or DTI could probably have enhanced the detection of trauma-related changes in the brain (Ashikaga et al. 1997, Kraus et al. 2007). Unfortunately, at the time of this study, these methods were not available. The volumetric MRI measures used in study III may indicate an atrophy caused by DAI, but without control values the findings remain uncertain.

Although DTI is a promising new tool to study the injured brain, the limitations of structural imaging should be acknowledged. Functional neuroimaging, such as functional magnetic imaging (fMRI), positron emission tomography (PET) and single photon emission computed tomography (SPECT) can visualize perfusion abnormalities in normal-appearing brain tissue after TBI (Garnett et al. 2001) and have a better association with the clinical outcome (Belanger et al. 2007).

6.2. Longitudinal cognitive changes after TBI

This was one of the few studies that focused on very long-term cognitive changes after TBI. It showed that a group of the subjects showed cognitive decline (60%), others either maintained (21%) or improved (23%) their cognitive level during the 30-year follow-up. Major risk factors for cognitive decline were male gender and higher age at injury. Whereas most cognitive domains declined, semantic memory behaved in the opposite way, showing good recovery potential.

To our knowledge, there are only few studies that have used objective longitudinal testing to investigate long-term cognitive impairments after TBI and our follow-up time was probably the longest. Thus, there is actually no comparable reference in the literature, although an interest in post-recovery cognitive decline after moderate-to-severe TBI has recently evolved (Till et al. 2008). Wood and Rutterford (2006) studied 74 people with mainly severe TBIs 16 years after the injury and compared their cognitive performance on WAIS to the original assessment (mean 1.05 years after TBI). Although they did find permanent cognitive impairment, they found no general decline between the original and

the follow-up assessment, only the oldest and those with the most severe injuries (21% of study cohort) declined, while 38% of the subjects improved their performance. The only risk factor for decline was a lower amount of education. In our study, educational level did not explain the cognitive change during the follow-up, but the level of education in our study group was fairly low and this may have contributed to the difference. Furthermore, contrary to our results, they did not find any improvement in the Similarities subtest of WAIS which is basically a semantic memory task. In study IV, we found that the improvement of semantic memory applied only to the subjects without the ApoE4 allele, whereas the ApoE4-positive group stayed at the same level as in the original assessment. The referred study by Wood and Rutterford did not control for the influence of this genetic factor. Furthermore, it is important to be aware that they used IQ (calculated with an only limited amount of subtests of WAIS) in the decline comparison, which is different from the MDB score we used. In IQ there are no tasks on episodic memory functions that are more sensitive to both TBI-related impairment and to normal cognitive aging (Craik and Jennings 1992, Nilsson 2003). Furthermore, the age of their subjects was much younger than ours (50 vs. 60 years at follow-up) and the evident age-related decline is not usually present during their follow-up period (18-50 years of age), especially when assessed only with IQ. Nor did they have a control group to compare the follow-up performance. This should be considered a flaw, since reference to population-based norms may not be representative of the TBI group in terms of age, gender, and educational background (Draper and Ponsford 2008). Our figures are also different from a shorter follow-up that showed that only 15% declined during the five-year follow-up (Millis 2001). Whereas methods and patient selection may contribute to this difference, it is reasonable that during a 30-year period, there will be more decline in certain cognitive domains, especially since a significant portion of our patients had reached the age of over 60 years during the follow-up.

Although there has been a debate about the possible cognitive decline and about the proportion of subjects at risk of the decline, most studies have found variable outcome after TBI. Millar et al. (2003) found that at 18 years follow-up after a head injury, twice as many patients had deteriorated (32%) as improved (15%) compared with how they were six months after the injury. The authors took the results as additional evidence for late decline (Lewin W et al. 1979, Klein et al. 1996). It is important to acknowledge that this latter study is not based on cognitive assessment, but the results come from a functional outcome measure (GOS-E). The different outcome measures are not directly comparable.

A recent prospective cognitive five-year follow-up found a decline in 30% of the subjects with moderate-to-severe injuries (Till et al. 2008). As the authors discussed, the

proportion and magnitude of decline observed in some subjects, as well as those of a small number of prior studies (Salmond et al. 2006, Millis et al. 2001, Hammond et al. 2004) in humans and animals (Bramlett et al. 2002, Dixon et al. 1999), are nontrivial. The study could not find any definite reasons for this post-recovery cognitive decline, but the decline was significantly correlated with the number of hours of therapy at five months post-injury. Importantly, increased rehabilitation was not confounded by severity of injury or initial severity of cognitive impairment, because there was no association between these factors and the amount of therapy provided. Furthermore, there was a trend, although not significant, that this decline was associated with alcohol abuse. The possible role of therapy to prevent cognitive decline of the patients at risk is interesting, and definitely worth further study. A causal link between the two could mean that post-acute apoptotic brain changes in white and grey matter could be at least partly experience-dependent (Robertson 2008). In our study material, only very few of the patients received systematic brain-injury-related therapy or neuropsychological rehabilitation, mainly because no services were available at the time of injury. Undoubtedly, the figures would have been more optimistic with better rehabilitation services. On the other hand, the basis of cognitive decline in our group may be different from the work of Till et al. (2008), since their subjects were younger and not likely to face the aging effect seen in our group.

The link between TBI and Alzheimer's disease has been studied intensively. The cognitive profile of our study group including improvement of semantic memory, and relative perseveration of delayed memory functions suggests a different cognitive pattern from that seen in the early phases of AD (Tierney et al. 1996). A subgroup of the patients (n=6, all males) developed subclinical or clinical dementia according to DSM-IV criteria, but without neuropathological confirmation it is impossible to say whether these patients had AD or whether the DSM-IV criteria were met due to the combined effect of TBI and aging (Isoniemi et al. 2006).

Another result of our study is that cognitive decline was associated with gender. Whereas women maintained their cognitive level, men declined during the follow-up (I Figure). The neuroprotective role of estrogen and progesterone has been intensively studied (Gibson et al. 2008, Vagnerova et al. 2008, Stein and Wright 2010, Khaksari et al. 2011), and the lower susceptibility in females with secondary brain injury has been observed in experimental models (Bayir et al. 2004). However, recent studies with clinical subjects have been conflicting (Ratcliff et al. 2007, Ponsford et al. 2008b, Liossi and Wood 2009, Brazinova et al. 2010). Most clinical studies are not designed to evaluate solely the effect of gender and, to our knowledge, no study has compared the cognitive change

between the genders truly long term after the injury. Thus, the combined effect of aging and TBI may well be more compromised in males than in females. Although the abuse of alcohol, as assessed with the SMAST, did not explain the cognitive change during the follow-up, we cannot rule out the effect of alcohol abuse on long-term cognitive decline after TBI, because it is well known that males use alcohol much more than females in Finland. Furthermore, it is difficult to get a real picture of the drinking habits by a short screening test like SMAST. This test does not give information about recent drinking or binge-type of drinking.

Altogether, there is an increasing amount of evidence that a subgroup of the subjects with TBI are facing late cognitive decline. As a group, their cognitive ability is still comprised compared with non-injured subjects, even decades after TBI (I: Table 2).

6.3 Cognitive functions in relation to MRI findings 30 years after TBI

The main result of the study was the association between MRI volumetric measures and impaired cognitive performance at the truly chronic phase after TBI (II: Table 3). Learning ability and memory functions, as well as the performance on the card sorting task, were associated with hippocampal volume and the volume of the lateral ventricle. More associations were found between cognitive functions and MRI volumetric measures than between cognitive functions and contusion findings on MRI. However, one of the most commonly reported cognitive impairments, the reduction in processing speed, was not associated with the MRI findings. The results are similar to the earlier reports that have found an association between hippocampal volume and the Index Score of the WMS. Thus, our results support the view that TBI may lead to permanent brain atrophy in the chronic stage, which has been related to a prolonged phase of post-acute atrophy after DAI (Ng et al. 2008).

Our results show that the atrophic signs seen in MRI volumetric measures are associated with memory functions in patients in the chronic phase after TBI, which is a finding similar to that of an earlier study with patients with more recent TBI (Bigler et al. 2002). When comparing these results to studies done in AD patients, it is important to note some discrepancies in the memory profiles between these two diagnoses. Whereas there have been studies showing a correlation between the hippocampal size and delayed memory tasks in AD patients (Reiman et al. 1998, Killiany et al. 2002), in these patients the hippocampal size was more clearly associated with the learning ability tasks. This suggests that an apparent structural similarity (hippocampal atrophy) does not necessarily mean

similar cognitive dysfunction. The hippocampus plays a crucial role in the consolidation of memory, and this function may be better preserved in the chronic phase after TBI than in AD.

Subjective evaluation of the everyday memory has not been a very reliable source of information when evaluating patients with a recent TBI, partly due to its lack of self-awareness commonly caused by TBI (Sunderland et al. 1983, Prigatano and Klonoff 1998). In the present study, there was a significant association between the self-evaluation of memory with a memory questionnaire and the volumetric MRI measure (left hippocampal volume, volume of lateral ventricle). This fits in with the clinical experience that the lack of self-awareness tends to diminish with time, particularly in terms of well-defined cognitive functions such as memory. Interestingly, patients with local contusions on MRI (either cortical or subcortical) did not differ from those without contusions in the total score of the memory questionnaire. In general, conventional structural imaging without volumetric analyses, whether by CT or MRI, rather poorly describes the well-being of patients in the chronic phase after TBI, both at group, but especially at individual level (Ichise et al. 1994, Ruff et al. 1994, Lee et al. 2008).

The Modified Wisconsin Card Sorting Test measures especially a domain of executive functions such as the ability to carry out mental shifts. There were associations between the total number of errors and perseverative errors in the MWCST and MRI volumetric measures. Especially the size of the lateral ventricle was a significant predictor for both kinds of errors. This is in line with the view that DAI tends to affect executive functions (Vilkki et al. 1994, Hanlon et al. 1999, Azouvi 2000, Scheid et al. 2006, Little 2010).

The other tests used here to evaluate executive and attentional functions were either time-dependent or time-limited, thus also measuring the information-processing speed. It is worth noting that the MRI findings were not associated with these tests, thus suggesting that brain pathology affecting the information-processing speed in TBI, in general, is perhaps poorly detectable by structural imaging.

Among the MRI measures used as predictors of cognitive functions, the most significant association was found between the volume of the lateral ventricle and the cognitive outcome. This association has been found earlier with recently injured patients (Gale et al. 1995), and thus this association may be a permanent feature after TBI. Compared to DAI, local contusions seem to have less influence on behavioral outcome even in a very long-term follow-up. Although not proven, it is apparent that the effect of local lesions is easier to compensate by a plastic mechanism than the possible long-lasting wide-spread process of DAI (Gale et al. 1995. Azouvi 2000, Bigler et al. 2002). In the present mate-

rial, the distribution of local contusions was fairly variable, which may also explain the relatively few associations with cognitive outcome. In general, dividing TBI into local or diffuse damage is somewhat arbitrary, since patients with local injuries also tend to have diffuse pathology as well (Reider-Groswasser et al. 2002, Garnett et al. 2000).

6.4 Attention and depressive symptoms in chronic phase after TBI

In this study, nearly all attention-related cognitive methods were sensitive enough to discriminate the TBI patients with depressive symptoms from the controls, and most tests were also sensitive enough to discriminate the non-depressive TBI patients from the controls. However, only few methods were capable of discriminating TBI patients with depressive symptoms from those patients without. The TBI patients with major depression (n=6) did not differ from the TBI patients without mood disorders in any cognitive method used, but this may well be due to insufficient statistical power, so this result should be regarded with caution.

Although the attention disorders after TBI and mood disorders with attention deficits are well-known separately, the association of a mood disorder and an attention deficit in patients with TBI is a complicated phenomenon. One pilot study suggests that post-TBI depression is associated with temporal lobe pathology, with concurrent delayed memory impairments, but not as clearly with frontal lobe pathology (Rao et al. 2010). Recent studies have suggested that the criteria for major depression should be used to evaluate the associations between mood disorders and cognition in patients with TBI (Rapaport et al. 2005, Chamelian et al. 2006). However, even though the prevalence of major depression in the acute phase after the injury is high, 26 – 28 % (Rapaport et al. 2005, Jorge et al. 1993), this figure may be different in the chronic phase of the injury. In fact, in our sample, the prevalence of major depression was high after the injury (26.7%), but only 10 % at the time of the current evaluation, 30 years after the injury (Koponen et al. 2002). The patients with chronic sequelae of TBI may also suffer from many other psychiatric conditions (Koponen et al. 2002, Bryant et al. 2010). Thus, using one strict psychiatric diagnosis, e.g. major depression, may not be the best way to evaluate the association between psychiatric disorders and cognition. In our study, we decided to use the short form of the Beck scale to dichotomise the TBI group into subjects with depressive symptoms and those without. By doing this, we got a sample size that allowed us to perform multiple comparisons.

Three computerized tests - simple reaction time, visual recognition speed of letters and the total hit rate in the vigilance test - differentiated the TBI patients with depres-

sive symptoms from those without. While the effect of TBI was widely seen in attention processing (e.g. Trail-making B, MWCST, verbal working memory tasks), the effect of depressive symptoms seemed to be limited to a narrow range of attention functions. Simple reaction time requires little complex cognitive processing and acted differently compared with most other attentional tasks (III: Figure 1): there was a significant difference between the group with depressive symptoms compared to those without, and at the same time, there was no difference between the TBI group without a mood disorder compared to the controls. This seems to support the idea that a specific prefrontal - subcortical circuit is linked to depression (Coffey et al. 1990, Sobin et al. 1997). These results also suggest that in TBI patients with chronic sequelae, the presence of depressive symptoms affects the more simple type of information processing or vigilance, while the effect of TBI is especially reflected in complex, flexibility- demanding processing, such as working memory, attention shifting, and executive functions. There is much evidence that major depression affects cognition (Merriam et al. 1999, Levin et al. 2001, Farrin et al. 2003) but it is interesting that also subclinical symptoms seem to have an impact on psychomotor speed and vigilance.

Reduction in speed of information processing was widely seen in our TBI patients, even in automatic processing (e.g. recognition of numbers and letters) that is not typically considered to be mediated by the frontal brain regions. Although TBI patients with depressive symptoms performed more slowly on the tasks, even the non-depressive TBI patients differed from controls. Traumatic axonal injury (Bigler et al. 2002, Flemingham et al. 2004) may form a basis for this finding. The developing atrophy caused by diffuse injury may affect the automatic processes, in contrast to the results from patients with mild, more recent injuries (Vilkki et al. 1994). Our results suggest that computerized methods for the evaluation of perceptual speed should be included in studies on cognitive functions of patients with TBI, especially in the chronic phase. This kind of widespread information processing slowness has also been documented in patients with other neurological disorders, such as multiple sclerosis (Kujala et al. 1994), which share the phenomenon of diffuse axonal injury (De Stefano et al. 2002). Slowness of information processing may be a factor that is a modifier to mood disorder after TBI.

The classic mind/body problem is particularly important from the medico-legal point of view, since insurance companies usually cover the damages when the cause of symptoms is the organic TBI, but not if they are considered to be caused, e.g. by reactive depression. This is at least the case in Scandinavia. Our results show that complex attention functions that are mediated by the frontal lobes are relatively independent of depres-

sive symptoms in the chronic phase after TBI, and that depression should not be considered a causative factor in all the cognitive deficits in the chronic phase after TBI. Although TBI and depressive symptoms are interrelated and may both affect cognitive functions, this study suggests that cognitively complex tasks requiring flexibility (e.g. MWCST, word fluency, working memory tests) are most specific to brain pathology caused by the TBI itself. These findings are supported by a recent study which concluded that post-TBI depression is associated with temporal lobe pathology, but not as clearly with frontal lobe pathology that is thought to mediate complex attentional functions (Rao et al. 2010). They also emphasize the importance of a comprehensive and careful neuropsychological assessment in the chronic phase after TBI.

6.5 Apolipoprotein E ε4 and cognitive functions after TBI

The presence of ApoE4 had an association with memory functions both post-acutely and decades later in subjects with TBI, but in different memory processes. In the original assessment, verbal learning was lower in the subjects with ApoE4, but after three decades, this association was no longer found. In the follow-up assessment, the presence of the ApoE4 allele was associated with poorer performance on working memory tests, while no associations were found in the speed of automatic processing or the simplest reaction time tests. Furthermore, the group with the ApoE4 allele made more errors on the visual memory test and had a poorer general cognitive level in the follow-up assessment. In a longitudinal comparison, there seemed to be improvement of semantic processing in subjects without the ApoE4 allele, while this was not apparent in the subjects with the ApoE4 allele. Also former studies have shown that there is an interaction between aging, ApoE, and memory functions (Wisdom et al. 2011, Beydoun et al. 2010), the mechanism of which is poorly understood but may be related to the role of lipids in myelination (Kadish et al. 2009). Our study suggests that TBI may modify these processes, thereby affecting this complex interaction.

These findings suggest that the role of the suspected genetic risk factor, the presence of ApoE4, may vary among different cognitive domains depending on the time interval after TBI, thus supporting the view of a temporal dynamic relationship between genetic factors and cognition (Han et al. 2007, Reichenberg et al. 2009). ApoE4 positivity, however, does not seem to have an effect on all cognitive domains, since visuomotor performance did not differ between the two ApoE groups in either assessment.

The association between verbal episodic memory and ApoE4 is the best-document-

ed finding between cognition and genetic factors, both in normal controls (Bondi et al. 1995, Berr et al. 1996, Caselli et al. 2009) and in subjects with TBI (Crawford et al. 2002, Sundström et al. 2004, Ariza et al. 2006). However, this poorer performance of TBI subjects with ApoE4 has been challenged by recent studies (Chamelian et al. 2004, Han et al. 2007, Ponsford et al. 2007). In our material, the association between ApoE4 positivity and verbal learning was found in the post-acute phase, but this association weakened during the follow-up so that the group with ApoE4 actually improved their performance, while, at the same time, their general cognitive level, as assessed with the MDB, decreased. The improvement in memory performance in subjects with ApoE4 is contrary to what has been reported with normal controls and may reflect a trajectory specific to TBI and its neuronal repair processes. These findings support the view that the presence of ApoE4 may have an adverse effect on learning and verbal episodic memory in the post-acute phase, but that this association weakens with time. Accordingly, another long-term follow-up study did not find difference between cognitive functions and ApoE4 status after TBI when using mainly verbal methods to assess memory and attention (Millar et al. 2003). The visual memory test (BVRT) we used is slightly more comprehensive than the visual reproduction of WMS used in their study, and our computerized methods have quite different cognitive demands than the Stroop and the verbal fluency tests used in their study to assess attention and information-processing speed. The results of directly comparable methods (WMS word associates, digit span) were similar between their study and ours, revealing no differences between ApoE4-positive and -negative subjects after a long-term follow-up.

Semantic memory, the memory system that includes concepts and meanings, is less often studied in subjects with TBI. Our recent study on longitudinal cognitive changes using the same study material, showed improvement of semantic memory as assessed with the similarities of the WAIS subtest (I). The findings of the present study suggest that this improvement applies only to the subjects without the ApoE4 allele, while the ApoE4 group remained at the same level, with no improvement being seen. The naming time of 20 objects, which also involves semantic processing, behaved similarly, showing a significant difference between the ApoE groups in the follow-up assessment. These findings suggest that the semantic memory, perhaps with more advanced testing methods, should be included in future research on long-term TBI consequences.

We were able to evaluate the study group with computerized methods that have been shown to be more sensitive to capture the subtle cognitive processing speed differences than conventional neuropsychological methods (Wilken et al. 2007). We found no differences between the ApoE groups in the simplest reaction time tasks or in automatic

processing speed. Differences were found, however, in the speed of working memory (the Subtraction time) that excludes the time spent on psychomotor involvement, covering only pure cognitive processing speed, and in the Ten-choice reaction time, both of which require more cognitive involvement than the simpler reaction time tasks. This suggests an association between the ApoE4 status and a reduction in complex cognitive processing speed. This would be worth further studies, also in the case of more recent TBIs and milder injuries with ApoE genotyping. The reduction in attentional functions and information-processing speed are meaningful consequences of TBI because they are likely to contribute to the failure to perceive emotional cues accurately and efficiently, and they may also compromise a subject's ability to track the continuous flow of data presented in social interactions (Bornhofen et al. 2008).

Although we were able to study a unique material of subjects with truly long-term follow-up and with comprehensive neuropsychological methods, there are several shortcomings one should be aware of when interpreting these results. First, we did not have a healthy control group to compare the findings with, either longitudinally or cross-sectionally. Therefore, we do not know how the ApoE4 status would be associated with cognitive functioning in normal controls during this kind of long-term follow-up. Secondly, the standard deviations are relatively large which may mean that not all ApoE4-positive subjects face an unfavorable cognitive outcome; it may be that only a certain subgroup of ApoE4-positive subjects explains these results (Isoniemi et al. 2006). Additional physiological factors may also be required in the relationship between ApoE status and cognitive performance (Puttonen et al. 2003). Thirdly, the sample size is relatively small to draw definite conclusions. Fourthly, there may be confounding factors, such as pre-injury and other unknown factors, that are not fully controlled, and these may have contributed to the results. Fifthly, the number of subjects with ApoE4 is relatively small, thus reducing the statistical power to detect differences reliably. On the other hand, the distribution of the ApoE genotypes of this sample corresponds closely to that of the general population of Finland, where 38.7% have the ApoE4 allele (Ehnholm et al. 1986). Furthermore, we feel that this sample well represents clinical patients with variable injury severity.

6.6 Risk factors for reduced survival after TBI

An important new finding of this study is that the reduced working ability was related to long-term reduced survival. Although there was no direct association between injury-related variables (e.g. injury severity and level of cognitive impairment) and reduced sur-

vival, there seemed to be an indirect involvement of these factors since those subjects who were not able to maintain their ability to work due to TBI had increased risk of death during the follow-up. In this indirect way, our results support the previously suggested association between cognitive consequences and reduced long-term survival (Brown et al. 2004, Harrison-Felix et al. 2004). An important finding was also that the late mortality was higher in the younger group of subjects (age < 40 years at death) compared with the general population (SMR 4.50, 95% CI=2.02-10.01). However, the total mortality rate did not differ significantly from the general population during the whole follow-up period (SMR 1.25, 95% CI=0.99-1.57). Thus, our first hypothesis was partially supported, but not in the case of the older patients. TBI seemed to have an adverse effect on the long-term vocational outcome, since working to normal retirement age seemed to be rare among the patients with TBI: only 11 % of the subjects continued working and fulfilled a normal working career after TBI.

Age at injury is an expected risk factor for reduced survival during a 30-year follow-up as the subjects were, on average, almost 40 years old at the time of TBI. In a way, this is such a strong explanatory variable that any other association that is not explained by age should be given careful attention. In our study, the vocational outcome had an independent explanatory role for reduced long-term survival. A change in the ability to work, measured either as a change to a less demanding job or premature retirement, is usually a reflection of both injury-related (cognitive impairment and injury severity) and demographic variables. The association between reduced working ability and long-term reduced survival has not been addressed in previous TBI studies, although one study has found employment at injury to be protective for long-term survival (Harrison-Felix et al. 2004). Our study supports the previous findings that TBI severity (as assessed with PTA and LOC) and cognitive impairment have a crucial impact on the vocational outcome after TBI (Stambrook et al. 1990, Green et al. 2008, Ponsford et al. 2008), also during long-term follow-up after TBI. Withdrawal from working life, together with chronic TBI symptoms may lead to psychological distress and/or untreated medical conditions that presumably shorten life expectancy. Due to the small number of subjects, we could not conduct any statistical analyses concerning the causes of death between the study group and the general population.

The diminished cognitive reserve caused by TBI has been suggested to lead to premature aging and earlier occurrence of degenerative brain disease (Satz 1993). In our material, we could not find a statistically significant association between the post-injury cognitive impairment, as assessed with the MDB, and reduction in survival, although there

was a trend (V: Figure 1) toward such an association. However, the increasing mortality in those with more severe cognitive impairment after 20 years of follow-up suggests that the lowered cognitive reserve hastens aging phenomena and predisposes to premature death at an older age, or that severe cognitive impairment predisposes to some other conditions that have an adverse effect on general health.

Our results concerning the late mortality after TBI are not comparable with the larger population-based samples studied earlier (Shavelle et al. 2001, Brown et al. 2004, Pentland et al. 2005, McMillan and Teasdale 2007, Cameron et al. 2008). However, our finding of a SMR of 1.25 (95% CI=0.99-1.57) is parallel with an earlier population-based report that found a slightly elevated death risk (mortality rate ratio 1.48, 95% CI=1.02-2.15) compared with the general population during a ten-year follow-up, after excluding the initial high-risk mortality period (Cameron et al. 2008). Although we did not find a generally high mortality risk as previously reported during the first seven years after TBI (McMillan and Teasdale 2007), we found an elevated mortality risk among the younger patients similar to that reported in the earlier study. The pre-injury characteristics (e.g. life-style factors, medical history) may explain a part of the elevated risk, although the risk has been shown to concern even patients without such characteristics (McMillan and Teasdale 2007, Cameron et al. 2008). There were unnatural deaths (two suicides and one homicide) among the subjects who died under 40 years of age. This is in accordance with a recent population-based study that suggested the possibility of premature deaths from suicides or accidents (Pentland et al. 2005). Accordingly, younger subjects may especially benefit from interventions aimed at adjusting to the injury burden in order to prevent risk behavior and depression. Age-group comparisons have not been included in most previous population-based reports. Our results are similar to those of studies that have taken this comparison into account (Flaada et al. 2007, McMillan and Teasdale 2007): the higher long-term risk of mortality for older subjects with TBI compared to non-elderly subjects mainly reflects the fact that age is an important predictor of death in persons without TBI. This is why the age factor is not given much attention in the survival analyses of our material. Information about longer term mortality seems to be largely missing from the TBI research. Our results suggest that there may be a continuing elevation of the mortality rate during the second decade after the injury, but that, thereafter, the mortality rates are likely to be closer to those of the general population. It has been reported that in Finland the initial TBI mortality rate is twice as high as in the other Nordic countries (Sundstrom et al. 2007). How this might affect the figures of later mortality is not known.

In the case of subjects with TBI, the task of finding a rough balance between the

requirements of work and the lowered cognitive abilities is difficult. Far too often these subjects return to work unaware of their cognitive and behavioral deficits. As noted earlier, both a long-term follow-up (Kreutzer et al. 2003) and a multifactorial approach (Walker et al. 2006) are crucial when evaluating working ability after TBI. Our long-term results are worrisome since the percentage of subjects (11 %) that continued to pursue an unchanged working career up to normal retirement age (63 years) was lower than expected. It is difficult to evaluate the findings in relation to other studies, given the differences in follow-up time, cultural factors, study material, and the variable definitions of working ability. Nor does this study give any definite answers or reasons for the late dropouts from working life. However, on the basis of our earlier studies of partly the same subjects, some may be vulnerable to late cognitive deterioration (I) or psychiatric illnesses such as depression (Koponen et al. 2002). Interestingly, our total percentage (26.5%) of subjects who continued to work to the normal retirement age (although in easier jobs) is similar to an earlier Finnish follow-up study of subjects with pediatric TBIs as preschoolers. The study showed that one third of the subjects were able to work full time at the average age of 40 years (Nybo et al. 2004, Nybo et al. 2005). The positive working outcome in their study was associated with better cognitive functions and with marital status compared with the non-working group. Otherwise, comparisons of the results are difficult due to the differences in study designs, in age, and in cognitive and statistical methods.

Of the various demographic factors, only age at injury was associated with vocational outcome in multivariate analyses. The association between education and vocational outcome seen in earlier studies (Dikmen et al. 1994) could not be confirmed in the multivariate analyses of the present study. This may be because, on average, the educational level of our group was fairly low. Abuse of alcohol was also associated with long-term vocational outcome. Alcohol abuse is often present before the injury; it is considered a major risk factor for TBI (Jennett et al. 1996), as well as for subsequent TBIs (Dischinger et al. 2001, Winqvist et al. 2008), and probably for post-acute cognitive decline after TBI (Till et al. 2008). One study suggested that there is a reduction in alcohol consumption during the first year after TBI, but a risk of increase thereafter (Ponsford et al. 2007). The combination of alcohol abuse and TBI consequences is definitely deleterious for the vocational outcome. Despite the cultural differences in drinking habits, international guidelines for active prevention of heavy drinking after TBI could be useful to improve the vocational outcome of subjects with TBI.

Although our findings are in accordance with the previous studies on the late mortality of subjects with TBI there are factors that should be considered. This study does not

describe the patients with multiple injuries because there were only six subjects known to suffer from such injuries. The subjects were admitted to the follow-up also due to an earlier injury, indicating that they had survived both the acute and the sub-acute period. Accordingly, it must also be noted that our results describe the late mortality after TBI, not the total mortality caused by TBI. There is also a certain amount of lost information from the initial material, which is a typical shortcoming in long-term follow-up studies. Another shortcoming in our study was the lack of systematic information about the subjects' pre-injury medical history, which might have influenced the results. It is also important to note that TBI rehabilitation services were not generally available during the 60's or 70's in Finland, so only few of the subjects received systematic TBI rehabilitation and this may have influenced the unfavorable vocational outcome and possibly the increased risk of reduced survival. On the other hand, the requirements of working life are nowadays much higher and the criteria for early retirement are slightly different from during those decades.

7. SUMMARY AND CONCLUSIONS

7.1 Conclusions

1. The cognitive outcome of the patients with TBI was variable after three decades. The majority of the patients showed a decline in their cognitive level, the rest either improved or stayed at the same level. Male gender and higher age at injury were significant risk factors for the decline. Whereas most cognitive domains declined during the follow-up, semantic memory behaved in the opposite way, showing good recovery potential after TBI.

2. The memory decline and impairments in the set-shifting domain of executive functions are associated with MRI-volumetric measures, whereas reduction in information-processing speed was not associated with the MRI findings. The presence of local contusions was only weakly associated with cognitive functions, suggesting that local lesions have less influence on long-term behavioral outcome than diffuse processes, such as DAI.

3. Complex attention functions and cognitive flexibility are relatively independent of depressive symptoms after TBI, although there may be domains of cognition that are more characteristic of mood disorders after TBI. The results suggest that in patients with TBI, the presence of depressive symptoms affects the more simple type of information processing or vigilance, whereas the TBI-related brain pathology especially affects working memory, attention shifting, and executive functions.

4. The presence of ApoE4 may be associated with different kinds of memory processes including verbal and visual episodic memory, semantic memory, and verbal working memory, depending on the length of time passed. Many other cognitive processes were not affected by the presence of ApoE4. Without a comparable follow-up with healthy controls, the role of TBI in the interaction between ApoE4 and memory decline remains obscure.

5. A reduced working ability, influenced by age-, injury- and lifestyle-related factors, is associated with long-term survival after TBI. The late mortality among younger patients is high, a finding which should be considered when planning the care after TBI.

7.2 Clinical implications and applications for further research

Cognitive impairments after TBI are present both post-acutely and decades after TBI. A careful assessment of different cognitive domains, with comprehensive cognitive methods, is important for a patient's lifelong journey with TBI. The cognitive impairments post-acutely are associated with reduced working ability, and they may indirectly mediate reduced survival after TBI. Furthermore, early and comprehensive neuropsychological assessment may facilitate awareness of the cognitive and behavioral consequences of the injury. It may help to recognize the cognitive reserve or domains of cognition that may show good recovery potential after TBI. The long-term cognitive course after TBI is highly variable, and further research with large prospective samples, with adequate control group and patient selection procedure, is needed to recognize patients at risk of late cognitive or behavioral decline or reduced survival. On the other hand, the purpose of this kind of study is to find factors that would enhance the cognitive and behavioral well-being of the patients with TBI.

Long-term cognitive impairments are, at least to some extent, associated with other medical factors such as MRI volumetric findings and the presence of ApoE4. The challenge for future work is to use even more sensitive neuroimaging and cognitive methods in order to improve the correlations between cognitive impairments and MRI findings. This would undoubtedly improve the diagnostic accuracy of the patients with TBI. Studies on the connection between cognition and ApoE genotypes would benefit from larger samples with control groups, which would also make gene dose analyses possible.

Understanding the evolvement of behavioral problems and cognitive impairments, and the interrelationship between these two, is especially important, since there is undoubtedly an overlap or a link between the two problems. Although invisible, they outstrip the other neurological consequences as the major cause of disability after TBI. The future task of neuropsychological rehabilitation may well be the reduction or prevention of secondary late-cognitive decline or secondary psychiatric conditions after TBI. Such work often starts with educating the patients and families about common cognitive and behavioral problems after TBI in order to achieve understanding and acceptance of the symptoms.

The results of this thesis further emphasize the importance and essentials of a multi-disciplinary approach to both life-long follow-up and care after TBI, and also to future research on long-term consequences of TBI.

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SHORT MICHIGAN ALCOHOL SCREENING TEST (SMAST)

NAME: _____ Date:_____

The following questions concern information about your involvement with alcohol during the past 12 months. Carefully read each countyment and decide if your answer is "YES" or "NO". Then, check the appropriate box beside the question.

Please answer every question. If you have difficulty with a countyment, then choose the response that is mostly right.

These questions refer to the past 12 months only.	**YES**	**NO**
1. Do you feel that you are a normal drinker? (by normal we mean do you drink less than or as much as most other people.)……		
2. Does your wife, husband, a parent, or other near relative ever worry or complain about your drinking?.....		
3. Do you ever feel guilty about your drinking?.....		
4. Do friends or relatives think you are a normal drinker?.....		
5. Are you able to stop drinking when you want to?.....		
6. Have you ever attended a meeting of Alcoholics Anonymous (AA)?.....		
7. Has your drinking ever created problems between you and your wife, husband, a parent or other near relative?.....		
8. Have you ever gotten into trouble at work because of your drinking?.....		
9. Have you ever neglected your obligations, your family, or your work for two or more days in a row because you were drinking?.....		
10. Have you ever gone to anyone for help about your drinking?.....		
11. Have you ever been in a hospital because of drinking?.....		
12. Have you ever been arrested for drunken driving, driving while intoxicated, or driving under the influence of alcoholic beverages?.....		
13. Have you ever been arrested, even for a few hours, because of other drunken behaviors?.....		
*** SMAST Score**……		

** See scoring instructions for correct scoring procedures.*

SHORT MICHIGAN ALCOHOL SCREENING TEST (SMAST)

Administration & Interpretation

Instructions

The Short Michigan Alcohol Screening Test (SMAST) is a 13-item questionnaire that requires a 7th grade reading level, and only a few minutes to complete. It was developed from the Michigan Alcoholism Screening Test. Evaluation data indicate that it is an effective diagnostic instrument, and does not have a tendency for false positives, as does the Michigan Alcoholism Screening Test. It is **strongly recommended** that the DAST-10 be used along with the SMAST unless there is a clear indication that the client uses alcohol but does not use any other drug at all.

The SMAST is self-administered. All questions are to be answered with "YES" or "NO" answers only.

Scoring: Each "YES" answer equals one (1) point.

Interpretations: A score of 1 or 2 indicates that there is no alcohol problem and no further action is needed at this time. A score of 3 indicates a borderline alcohol problem and further investigation is necessary. A score of 4 or more indicates that there may be an alcohol problem and that a full assessment is needed.

SMAST Score	Degree of Problem Alcohol Involvement	Suggested Action
0-2	No problems reported	None at this time.
3	Borderline alcohol problem reported	Further investigation is required.
4 or more	Potential Alcohol Abuse reported	A full assessment is required.