Clinical utility of cognitive Event Related Potentials (ERP) in severe acquired brain injury - diagnostic value of ERP in prolonged disorders of consciousness and prognostic utility in the sub-acute phase after very severe traumatic brain injury

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Table of contents

ACKNOWLEDGMENTS	4
LIST OF ABBREVIATIONS	6
GENERAL SUMMARY	7
LIST OF PAPERS	
INTRODUCTION	
THE MATTER OF CONSCIOUSNESS	
Historical perspectives	
A new era for a science of consciousness	
Brain structures and networks involved in consciousness	13
HISTORICAL OUTLINE OF DISORDERED CONSCIOUSNESS IN SEVERELY BRAIN-INJURED PATIENTS	
ESTABLISHMENT OF EMPIRICALLY BASED DIAGNOSTIC CRITERIA	14
The neurobiological underpinnings of DoC	
CHALLENGES IN DIAGNOSING DOC	20
Inferring consciousness in patients with DoC	
The risk of misdiaanosis in patients with DoC	
Differential diaanosis	
RECOVERY AND TREATMENT OPTIONS IN DOC	
Recovery and prognosis in patients with DOC	2.3
Treatment ontions for natients in DoC	2.4
Sensory stimulation pharmacological interventions and brain stimulation treatment	2.4
PROGNOSTIC CHALLENGES IN SEVERE TBI	26
THE DIACNOSTIC AND PROGNOSTIC UTILITY OF MODERN NEUROSCIENTIFIC METHODS	20 27
Figure Related Potentials (FRPs)	<u>2</u> , 28
The auditory N1 and the mismatch-negativity	20
The D2 component - FRD in detecting consciousness	
Prognostic usefulness of electron busicleavin severe brain injury	
MAIN RESEARCH OBJECTIVES	34
METHODS	35
DESIGN	35
PARTICIPANTS	36
Procedures	37
ERP-experimental paradigm and procedures	37
EEG-recordings	
Methods for systematic review	
Neuropsychological test measures and questionnaires for functional outcome	
STATISTICAL ANALYSIS	40
ETHICAL CONSIDERATIONS	42
SUMMARY OF PAPERS	43
Paper I	43
PAPER II	45
PAPER III	46
DISCUSSION	47
DIAGNOSTIC UTILITY OF ELECTROPHYSIOLOGICAL METHODS IN PATIENTS WITH DOC	
ERP and the robustness of two distinct active tasks	
-	

Diagnostic accuracy of electrophysiological methods in patients with DoC	50
False negatives and -positives in detecting electrophysiological signs of command-follo	wing50
PROGNOSTIC UTILITY OF COGNITIVE ERPS IN SEVERE TBI	52
Use of ERP in detecting sub-acute signs of residual cognitive capacity	52
Association between sub-acute P3 response in active task and outcome	53
Outcome diversity in patients with severe TBI	53
METHODOLOGICAL ISSUES	54
Interpretation of negative electrophysiological findings	54
Active ERP-tasks with requirements for language perception	55
Variation in electrophysiological techniques and tasks across studies	55
The issue of blinding in electrophysiological studies probing for residual cognition	56
Patients sample sizes	57
The electrophysiology of lesioned brains	57
CLINICAL IMPLICATIONS	58
CONCLUSION AND FUTURE DIRECTIONS	60
REFERENCES	61

And men should know that from nothing else but from the brain came joys, delights, laughter and jests, and sorrows, griefs, despondency and lamentations. And by this, in an especial manner, we acquire wisdom and knowledge, and see and hear and know what are foul, and what are fair, what sweet and what unsavory . . . —The Hippocratic Writings

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List of abbreviations

BAEP	Brain Auditory Evoked Potential	
BCI	Brain Computer Interface	
CAP	Confusion Assessment Protocol	
CI	Confidence intervals	
CMD	Cognitive motor dissociation	
CRS-R	Coma Recovery Scale-Revised	
CWIT	Color-Word Interference Test	
DAI	Diffuse axonal injury	
DoC	Disorders of consciousness	
DRS	Disability Rating Scale	
DTI	Diffusion Tensor Imaging	
EEG	Electroencephalography	
ERPs	Event Related Potentials	
fMRI	Functional magnetic resonance	
	imaging	
GCS	Glasgow Coma Scale	
GOSE	Glasgow Outcome Scale-Extended	
ICA	Independent Component Analysis	
ICU	Intensive care unit	
LIS	Locked-in syndrome	
MCS	Minimally conscious state	

MCS- Minimally conscious state minus

- MCS+ Minimally conscious state plus
- MMN Mismatch-negativity
- NCC Neural correlate of consciousness
- NCS-RNociception Coma Scale-Revised
- OUH Oslo University Hospital
- PCI Perturbational Complexity Index
- PET Positron emission tomography
- PTCS Post-traumatic confusion
- QUADAS-2 Quality Assessment of Diagnostic Accuracy Studies-2
- SEP Somatosensory evoked potential
- SON Subject's own name
- TBI Traumatic brain injury
- tDCS transcranial direct current stimulation
- TMS Transcranial magnetic stimulation
- UN Unfamiliar name
- UWS Unresponsive Wakefulness Syndrome
- VS Vegetative state
- WASI Wechsler Abbreviated Scale of Intelligence

General Summary

Over the past decades, advancements in emergency medicine and lifesaving technologies have led to an increased number of patients who survive the most severe acquired brain injuries. Given that they survive the initial phase, patients will typically suffer from a transient state of coma, with loss of consciousness, eyes closed and with no sleep-wake cycle. After awakening from coma, many patients will evolve into a period with disordered consciousness (DoC) on their way to further recovery, although with highly variable recovery trajectories. However, a minority of patients remain in a state of prolonged, and sometimes lifelong DoC. Consensus regarding diagnostic criteria for the vegetative (VS) and minimally conscious states (MCS) has existed since 2002. This has allowed for a tremendous increase in research regarding patients with DoC, including standardization of behavioral diagnostic assessments tools. While the VS is characterized by intermittent wakefulness in the absence of any behavioral signs of awareness, MCS is characterized by the presence of unequivocal behavioral evidence of awareness of the self or the environment, although these responses typically fluctuate and are inconsistent. Distinguishing patients who show behavioral signs of awareness through volitional responses, from unconscious patients with only reflexive behaviors remains, however, clinically challenging. Even with the most careful and standardized assessment performed by experts, signs of awareness can be missed because the clinical diagnosis relies on motor signs of awareness that can be subtle and fluctuate over time. An additional major clinical concern is the lack of accurate prognostic tools for patients with the most severe brain injuries. At present, predicting survival, outcome and long-term cognitive deficits at an individual level in severely brain-injured patients is very difficult. Hence, health care professionals face major challenges both in diagnostic and prognostic assessments regarding this patient group, which is critical for making the correct decisions regarding acute medical care, level of treatment and rehabilitation efforts, as well as informing the families on realistic expectations regarding recovery.

New developments within neuroscientific methods have given increased insight into brain characteristics of severely brain-injured patients, included those in VS and MCS. Modern neuroimaging and neurophysiological techniques have shown promising results in detecting markers of consciousness and prognostication in patients surviving the most severe brain injuries. This has led to optimism for the utility of these techniques with regard to diagnostic and prognostic considerations.

This thesis investigates the clinical diagnostic utility of event related potentials (ERPs) in patients with DoC following acquired brain injury, as well as the prognostic utility of subacutely recorded cognitive ERPs following very severe traumatic brain injury (TBI). In paper I, the diagnostic utility of ERP was examined by applying two active ERP-tasks with different cognitive load in a group of patients with stable MCS, as well as in a group of neurologically healthy subjects. The results showed that the active task, with the instruction to count the subject's own name (SON), elicited higher rates of electrophysiological signs of commandfollowing compared to the active task with instruction to listen for a change in pitch. This was demonstrated both in the healthy control group and in the patients in MCS, suggesting that the counting of SON was the most robust task in probing for command-following without motor responses. Moreover, five of 11 patients in MCS who did not demonstrate behavioral command-following, displayed electrophysiological signs of command-following in the counting task, denoted false positives. In this context, false positives can suggest that some patients with DoC may have remnant cognitive capacities not demonstrated behaviorally. In summary, these findings support previous studies, which have indicated that an ERP-task with the instruction to count SON is superior to the pitch-task, with a higher sensitivity in detecting electrophysiological indices of command-following in patients with DoC.

In paper II, the clinical diagnostic utility of electrophysiological techniques in patients with DoC was investigated in a systematic literature review. It included scientific papers investigating electrophysiological signs of command-following by applying active tasks in patients with DoC. In the twenty-four studies found eligible and included, estimated sensitivity rates in healthy controls ranged from 71% to 100%, demonstrating variable accuracy across studies. In patients with DoC, both specificity and sensitivity rates varied highly, both ranging from 0% to 100%, with the two largest studies included in the systematic review demonstrating false positive rates of 17% and 33%. In summary, paper I and paper II support the notion that electrophysiological signs of covert command-following can be detected in a minority of patients with DoC, but also demonstrate that a considerable number of patients who display behavioral signs of consciousness do not do so electrophysiologically (false negatives).

In paper III, the prognostic utility of cognitive ERPs recorded sub-acutely following very severe TBI was investigated. The results showed that 10 of 14 patients demonstrated a significantly enhanced cognitive P3 in the active task with instruction to count SON compared to passive listening across three repeated sub-acute recordings. Six patients demonstrated normalization of the P3 component in the counting task. Moreover, P3-amplitude to the counting task at the third recording was positively correlated with both functional outcome and cognition six months post-injury. These results suggest that ERP can index cognitive P3 component recorded in the early phase after severe TBI may provide supplementary prognostic information, but further studies with larger samples are needed to investigate the prognostic accuracy of cognitively mediated ERPs.

In summary, the findings presented in this thesis support the notion that ERP may supplement standard behavioral diagnostic assessments in revealing covert signs of consciousness in a minority of patients with DoC. However, we are still far from establishing standard guidelines for clinical implementation of electrophysiological methods, and there is a high risk of false negatives, that is, patients showing no electrophysiological signs of command-following despite clear behavioral signs of such capacity. Moreover, the findings indicate that ERP can inform on regained cognitive capacities in the sub-acute phase after severe TBI, and may yield supplementary prognostic information, but there is to date a lack of sufficient knowledge regarding sensitivity and specificity rates for prognostic accuracy of cognitive ERPs.

List of papers

The thesis is based on the following papers, referred to in the text by their Roman numbers I-III.

Paper I

Hauger, S.L., Schnakers, C., Andersson, S., Becker, F., Moberget, T., Giacino, J.T., Schanke, A.K., Løvstad, M. (2015). Neurophysiological indicators of residual cognitive capacity in the minimally conscious state. *Behavioural Neurology*.145913. doi: 10.1155/2015/145913

Paper II

Hauger, S.L., Schanke, A.K., Andersson, S., Chatelle, C., Schnakers, C., Løvstad, M. (2017). The clinical diagnostic utility of electrophysiological techniques in assessment of patients with disorders of consciousness following acquired brain injury: a systematic review. *J. Head Trauma Rehabil.* 23. doi: 10.1097/HTR.00000000000267

Paper III

Hauger, S.L., Olafsen. K., Schnakers, C., Andelic, N., Nilsen, K.B., Helseth, E., Funderud, I., Andersson, S., Schanke, A.K., Løvstad, M. (2017) Sub-acute cognitive event related potentials following severe traumatic brain injury – presence and normalization of the P3 response, and it's relationship to outcome *J. Neurotrauma*. 7. doi: 10.1089/neu.2017.5062

Introduction

The matter of consciousness

Historical perspectives

The struggle to comprehend the interaction between mind and body is ancient old, and early Western philosophers like Descartes (1596-1650) and Locke (1632-1704) maintained a dualistic approach to the understanding of consciousness, separating the body as material and the mind (or soul), on the other hand, as nonmaterial (Hergenhahn, 1992a). Today, it is commonly understood that it is the brain that gives rise to our consciousness. Plum and Posner define consciousness as "the state of full awareness of the self and one's relationship to the environment" (Plum & Posner, 2007). The neuroscientist, Christof Koch states: "without consciousness there is nothing. The only way for you to experience your body and the world of mountains and people, trees and dogs, stars and music, is through your subjective experience, thoughts, and memories" (Koch, 2012, p. 22). He refers to the most difficult aspect of consciousness, the so-called 'hard problem' of gualia, how physical matter and sensation can give rise to the non-physical, subjective experience of the redness of red and the painfulness of pain. In the early days of psychology, as it aspired to be an empirical science, scientists viewed consciousness with skepticism, where consciousness was regarded as unavailable for empirical study. Even in the more recent era of behaviorism, consciousness was regarded as the "black box", where psychologists and scientists, such as Pavlov (1849-1936), strived for an objective study of human behavior, and were not occupied with internal processes related to subjective consciousness (Hergenhahn, 1992b). On the other hand, in contemporary psychology and neuroscience, consciousness has become a significant topic of research (Crick & Koch, 1992). The interrelationship between the mind and body, as to how the *experience* of the redness of red can arise from the biological actions of the brain, is however, still not fully understood. As noted, this subjectiveness, or first-person experience of consciousness has been denoted as the "hard problem" of consciousness (Chalmers, 2013), and lies in our inability to explain experience. Some, such as the philosopher Thomas Nagel, known for his pessimism about science's ability to explain the subjectiveness of conscious experience, have thus advocated that consciousness is scientifically intractable. In his seminal 1974 essay "What is it like to be a bat?", he argues that one cannot entirely know how the sentience of *being* someone else, and takes the example of a bat, which has fundamentally

different neural organization than ourselves, meaning that it is not possible to directly compare third-person observations and sensations (Nagel, 1974).

A new era for a science of consciousness

What has been denoted the "easy problem" of consciousness refers to third-person data (Chalmers, 2013). This involves behaviors and brain processes of conscious systems that can be explained and studied with standard methods of cognitive science in terms of computational or neural mechanisms. An example of an easy problem would thus be the neural functioning of the brain system for perceptual discrimination of external stimuli, i.e. brain signals for perception of the smell or visualization of a flower (Chalmers, 2010, 2013). A proposed goal for many neuroscientists engaged in the understanding of consciousness, such as Crick and Koch (Crick & Koch, 1998), is to follow the footprints of consciousness in the brain by ultimately identifying it's underlying neural substrate. Crick and Koch have called this quest for the neural underpinning the "neuronal correlates of consciousness" (NCC). NCC is understood as the minimal neuronal mechanisms that are jointly sufficient for any one specific conscious percept (Crick & Koch, 1995, 1998, 2003). Thus, every phenomenal, subjective state will have an associated NCC: one for seeing a red patch, another for seeing a dog, a third for hearing a singing bird and so on. Although a generally accepted theoretical framework for understanding the concept of consciousness is still lacking, some theories have become widely recognized. The Global Neuronal Workspace theory (Baars, 2005) states that conscious perception depends on "ignition" of a fronto-parietal workspace that globally broadcasts information (Boly et al., 2012). According to the Integrated Information Theory, consciousness corresponds to the capacity of a system to integrate information (Massimini et al., 2005; Tononi, 2004). This theory starts from phenomenology of consciousness, that is, the subjective experiences, and claims that the neural substrate of human consciousness is a system that is both integrated (it cannot be subdivided into components that are experienced independently) and differentiated (it has a large repertoire of available conscious experiences). However, the scientific field of understanding the neural underpinnings of the whole concept of consciousness is at an early stage (Crick & Koch, 2003; Oizumi, Albantakis, & Tononi, 2014).

Mirroring the philosophical question of what it is like to be a bat, Laureys and Boly published a paper entitled "What is it like to be vegetative or minimally conscious?" (Laureys & Boly, 2007). They put forward questions like: "What is it like to be a patient in a state with disordered consciousness?"; "Can patients with DoC experience suffering or satisfaction?"; "What is their quality of life?"; "Is their way of perceiving the world in any way comparable to our own?" In parallel with the development of modern scientific methodology, a great increase in scientific interest has taken place with respect to patients with DoC following severe acquired brain injury. The question of what it feels like to be minimally conscious has yet to be understood, although modern neuroscientific methodology has greatly increased our understanding of both human brain processing and the neurobiological substrates of consciousness, leading to improved care and management of patients suffering from the most severe brain injuries.

Brain structures and networks involved in consciousness

"The brain is a democracy –there is no such thing as a prince or a pope, who sees and hears everything, and takes all decisions –no privileged seat of consciousness, no pontifical seat", Giulio Tononi wrote metaphorically about the biological organization of consciousness in the brain (Tononi, 2012, p. 30). Which brain structures that are essential for consciousness is still a matter of debate, and several cortical and sub-cortical regions seem to be involved. Thus, it has been argued that there is not a particular singular brain structure responsible for producing consciousness, but instead cooperation of multiple network ensembles involving many parts of the brain is a prerequisite for conscious perception (Blumenfeld, 2016; Koch, 2012). Important medial cortical areas involve the median frontal and parietal, as well as anterior and posterior cingulate cortices. On the lateral surface, networks involving lateral and orbital frontal, anterior insula, and lateral temporal-parietal association cortex are central for consciousness. These higher-order association cortices interact with sub-cortical structures involved in arousal, such as the midbrain and upper pons, thalamus, hypothalamus and the basal forebrain (Blumenfeld, 2016).

Historical outline of disordered consciousness in severely brain-injured patients

Prior to the medical advancement for resuscitation and intensive care unit treatments in the 1950s, patients with the most severe brain injuries producing coma rarely survived. As such, the clinical categories of vegetative and minimally conscious state were only recognized at a later stage. The diagnostic category "persistent vegetative state" (PVS) was first introduced in 1972 by Jennett and Plum to describe surviving patients who exhibit no behavioral signs of self or environmental awareness, but are awake and have sufficient preservation of autonomic

functions (e.g., respiration, heart rate, temperature regulation) to sustain survival when appropriate supportive care is provided (Jennett & Plum, 1972). The term "persistent" was added to denote that the condition remained present for more than one month after the injurious insult. At that point, medical knowledge about this patient group was sparse, and no treatment guidelines to improve their conditions existed (Jennett & Plum, 1972). In 1994, a retrospective review of all published studies involving this patient group lead to criteria for the temporal boundaries of irreversibility of the vegetative state, denoted as the "permanent vegetative state" (The Multi-Society Task Force on PVS, 1994). Based on the report of The Multi-Task Force on PVS, the American Academy of Neurology concluded that after three months following a non-traumatic injury and twelve months after a traumatic injury, the vegetative state (VS) was considered permanent, based on probabilities with high degree of clinical certainty (The Quality Standards Subcommittee of the American Academy of Neurology, 1995). It is important to underline that use of the term "permanent" is challenged today, as it denotes irreversibility, whereas long-term recovery is sometimes seen, especially in non-anoxic injuries (Giacino, Katz, & Whyte, 2013).

Of note, up until the 1990s, few distinctions were made between awake, but non-conscious patients and those showing subtle and inconsistent signs of being aware of themselves or their environment (Giacino, 2004). The categorization of the minimally conscious state (MCS) was introduced in the late 1990s (Giacino, 1997). By then it had been recognized that confusion in terminology and lack of extended observation for behavioral evidence of consciousness caused misdiagnosis by overlooking subtle and inconsistent signs of consciousness, and that presence of physical and sensory disabilities could confound accurate diagnosis (Andrews, Murphy, Munday, & Littlewood, 1996; Childs, Mercer, & Childs, 1993). No sensitive assessment tools for evaluation of level of consciousness existed at that time, and neuropsychologists did not routinely engage in clinical assessment of these patients, as they were typically considered "untestable".

Establishment of empirically based diagnostic criteria

The diagnostic entity of minimally conscious state was not established until 2002 (Giacino et al., 2002), thus, distinguishing patients in a vegetative state from patients showing minimal and fluctuating behavioral signs of consciousness. The establishment of operational criteria for DoC has since allowed for substantial improvement in diagnostic accuracy, development

of standardized assessment tools with good psychometric properties, and a vastly increased volume of research (Giacino, 2004; Gosseries, Zasler, & Laureys, 2014).

The following section summarizes the recommendations of definitions and diagnostic criteria for the VS and the MCS, published by the Aspen Workgroup in 2002 (Giacino et al., 2002). VS, also referred to as the "unresponsive wakefulness syndrome" (UWS; Laureys et al., 2010), is characterized by intermittent wakefulness in the absence of any behavioral signs of awareness, and all of the criteria summarized in table 1 must be met (Giacino & Whyte, 2005). On the other hand, MCS is characterized by the presence of inconsistent, but clearly discernible behavioral evidence of awareness of self or the environment (Giacino et al., 2002). The diagnosis of MCS requires unequivocal evidence of one or more of the following behaviors: simple command following; gestured or verbal yes/no responses; intelligible verbalization; and movements or affective behaviors that occur in contingent relation to relevant environmental stimuli and are not attributable to reflexive activity. Any of the following examples provide sufficient evidence for contingent behavioral responses: episodes of crying, smiling, or laughter in response to the linguistic or visual content of emotional, but not neutral topics or stimuli; vocalizations or gestures that occur in direct response to the linguistic content of comments or questions; reaching for objects that demonstrates a clear relationship between object location and direction of reach; touching or holding objects in a manner that accommodates the size and shape of the object; and or pursuit eye movement or sustained fixation that occurs in direct response to moving or salient stimuli (Giacino & Whyte, 2005, p. 33).

It has recently been suggested to divide the MCS entity into MCS+ and MCS-, depending on the complexity of behavioral responses. While MCS+ is characterized by more complex cognitive capacities, i.e. presence of command-following, MCS- is characterized by nonlinguistic and simple signs of conscious awareness, see table 1. Consensus on a clear definition of MCS+ and MCS- is however, currently lacking (Bruno et al., 2012; Bruno, Vanhaudenhuyse, Thibaut, Moonen, & Laureys, 2011), and the distinction is in need of further validation.

A traumatic brain injury (TBI) is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force (Menon et al., 2010). After a TBI, patients

who survive the initial acute phase and awaken from coma, will typically progress in recovery from a period of impaired consciousness to an acute confusional state, termed posttraumatic confusional state (PTCS; Sherer, Nakase-Thompson, Yablon, & Gontkovsky, 2005), typically followed by further improvement (Povlishock & Katz, 2005). Although VS and MCS represent transitory states on the way towards full recovery of consciousness for most patients, a minority with severe acquired brain injury remain in a state of DoC for prolonged and sometimes life-long periods (Beaumont & Kenealy, 2005; Leonardi, Sattin, & Raggi, 2013). Incidence studies of DoC are sparse, but Nordic European countries have reported estimates of annual incidence rates varying from 0.13-0.3 per 100 000 sustaining DoC three months after severe traumatic brain injuries, reduced to 0.02-0.14 per 100 000 after one year (Godbolt et al., 2013; Lovstad et al., 2014). Recent systematic reviews of prevalence of DoC have estimated 1.5 per 100 000 for MCS and 0.2-6.1 per 100 000 for VS (Pisa, Biasutti, Drigo, & Barbone, 2014; van Erp et al., 2014). However, the reliability of the prevalence estimates is questionable, as several of the studies included pre-dated the MCS diagnostic criteria established in 2002 (Giacino et al., 2002). However, it is without doubt the case that the DoC-population represents a low-frequency, but very severe and cost-intensive patient group. Moreover, patients with severe acquired brain damage present unique challenges regarding diagnosis, prognosis, treatment and clinical management, both acute and postacutely, as well as in the chronic phase.

Table 1. Classifications of disorders of consciousness following severe acquired brain injuries

Clinical entities	Definitions
Coma	No wakefulness
(Plum and Posner, 2007)	No awareness of self or environment
Vegetative state/unresponsive	Intermittent wakefulness
wakefulness syndrome	No awareness of self or environment
(Giacino & Kalmar, 2005;	No evidence of sustained, reproducible, purposeful
Laureys et al. 2010)	behavioral responses to external stimuli
	No language comprehension or expression
	Sufficient preservation hypothalamic and brain stem
	autonomic functions
	Bowel and bladder incontinence
	Variably preserved cranial-nerve and spinal reflexes
Minimally conscious state	Wakefulness
(Giacino et al. 2002)	Fluctuating awareness with unequivocal evidence of
	reproducible, purposeful behavioral responses to
	external stimuli
Minimally conscious state	Visual pursuit
minus	Reaching for objects
(Bruno et al. 2011)	Orientation to noxious stimulation
	Contingent affective behaviors
Minimally conscious state	Command-following
plus	Intelligible verbalization
(Bruno et al. 2011)	Intentional communication, i.e. gestural or verbal yes/no
	responses
Emergence from minimally	Functional communication
conscious state	Functional object use
(Giacino et al. 2002)	

Table adapted from Gosseries et al., (Gosseries, Di, Laureys, & Boly, 2014).

The neurobiological underpinnings of DoC

All severe brain injuries produce widespread deafferentation and reduced input to neurons across the cortico-thalamic system (Giacino, Fins, Laureys, & Schiff, 2014). The mesocircuit model (Figure 1), proposed by Schiff (2010), suggests that the anterior forebrain function is markedly downregulated in all severe brain injuries as a result of widespread disconnection or neuronal death. The model emphasizes the role of thalamocortical and thalamostriatal outflow reduction due to deafferentation and loss of neurons from the central thalamus. This causes a consequent withdrawal of important afferent drive to neurons of the striatum, which may then fail to reach firing threshold because of their requirement for high levels of synaptic background activity. Subsequently, the loss of active inhibition from the striatum allows neurons of the globus pallidus interna to tonically fire and thus provide active inhibition to their synaptic targets, including neurons of the already strongly inhibited central thalamus (Shiff et al., 2010; Giacino et al., 2014). These networks underpin functions for controlling arousal level, focusing attention, and initiating, sustaining and shifting behavior (Giacino et al., 2013), and it is proposed that DoC arises in the context of partially disconnected corticothalamic systems (Giacino et al., 2014). Studies have shown significant changes in cerebral metabolism in MCS patients compared to normal subjects, with resting global metabolic rates measured near ~50% of normal (Laureys et al., 2004; Schiff et al., 2005). Also in VS, PETstudies have shown massive decreases in brain metabolism about 40–50% of normal values, which may decrease further in the course of their injury (Laureys, Faymonville, Moonen, Luxen, & Maquet, 2000; Laureys & Schiff, 2012).



Figure 1: The mesocircuit model (Giacino et al., 2014). Reprinted with permission. 18

In a post-mortem analysis by Jennett and colleagues (Jennett, Adams, Murray, & Graham, 2001), a group of 35 individuals who remained in post-traumatic VS until death was compared to a second group of 30 patients with MCS or emerged MCS (12 MCS and 18 emerged from MCS, but remained severely disabled) until the time of death. While all patients in the VS group had moderate to severe diffuse axonal injury (DAI, grade 2 to grade 3) and/or lesions involving the thalamus, 50% of the group with severely disabled patients had no evidence of grade 2 or 3 DAI and no indication of thalamic damage. In the MCS group, 42% had moderate to severe DAI (versus 22% in the severe disabled group). In the group of VS, on the other hand, both moderate to severe DAI (71%) and thalamic lesions (80%) were much more frequent.

Patients in VS may be left with islands of partially functioning brain areas, which can for example, result in production of an isolated word, or an isolated movement, but not occurring in a contingent relation to relevant environmental stimuli, and therefore not considered to be volitional (Schiff et al., 2002). Studies applying event related potentials (ERP) have also shown that passive tasks without demand of active mental processing, can elicit ERP responses, e.g. the P3 wave, even in patients in coma or VS (Fischer, Luaute, & Morlet, 2010a; Perrin et al., 2006). The VS has therefore been denoted as a disconnection-syndrome (Laureys, 2005), where islands of partially functioning brain areas are disconnected and disintegrated from the networks needed for conscious cognition. Hence, preserved wakefulness networks of the brainstem and basal forebrain characterize patients in VS, while the cerebral networks accounting for subjective awareness are disrupted. Figure 2 illustrates the spectrum of disorders of consciousness as defined by the relationship between arousal and awareness.



Figure 2. Comatose patients cannot be aroused and, hence, are not aware of the environment or of them selves. The minimally conscious state characterizes patients whom demonstrate inconsistent, yet reproducible behavioral evidence of awareness of self or environment, but are unable to communicate their thoughts and feelings. The locked-in syndrome describes patients who are awake and conscious, but can only communicate by using small eye movements (Demertzi et al., 2008). Reprinted with permission.

Specifically, networks serving "external awareness" encompassing lateral fronto-temporoparietal cortices bilaterally, and neural network for "internal awareness" including midline anterior cingulate/mesiofrontal and posterior cingulate/ precuneal cortices, have been found to be functionally disconnected in VS (Demertzi, Soddu, & Laureys, 2012). In contrast, a partial preservation of the large-scale associative frontoparietal network has been demonstrated in patients in MCS (Laureys et al., 2004). In addition, PET studies applying nociceptive stimuli in patients with DoC have demonstrated activation of the pain matrix in patients in MCS similar to that observed in healthy controls, whereas brain activation to nociceptive stimuli in VS was limited to primary sensory areas, but did not activate the associative cortices involved in subjective pain perception (Boly et al., 2008), confirming a dissociation of brain areas necessary to produce awareness of internal and external events.

Challenges in diagnosing DoC

Inferring consciousness in patients with DoC

In describing DoC clinically after severe brain injuries, consciousness is typically explained as consisting of two main components: arousal, as in wakefulness or vigilance, and awareness, as in the content of consciousness and awareness of the environment and of the self (Laureys, 2005). Awareness can be divided into "external awareness", such as sensory or perceptual awareness of the environment, and "internal awareness", as in stimulus-independent thoughts, mental imagery, inner speech, or mind wandering (Vanhaudenhuyse et 20

al., 2011). Giacino emphasized early on that in addition to the basic elements of wakefulness and the capacity to detect and perceptually encode interoceptive and exteroceptive stimuli, consciousness also encompasses the capacity to formulate goal-directed behavior (Giacino, 1997). When assessing level of consciousness in the clinical setting, arousal is measured by eye-opening and the level of attention, whereas awareness is assessed by the patient's non-reflexive voluntary responses, for example command-following, visual pursuit or orientation to noxious stimulation.

The risk of misdiagnosis in patients with DoC

Today, bedside examination is the standard of clinical assessments, although, there is no consensus for standardized evaluation procedures for the clinical examination of patients with DoC (Giacino et al., 2013). Despite improvements in establishing diagnostic categories of DoC, rates of misdiagnosis have been reported to be as high as 41% if standardized assessment tools are not used, even if clinician-based consensus is established between experienced neurorehabilitation professionals. The bias is still in the direction of not detecting signs of consciousness, thus overestimating VS (Schnakers, Vanhaudenhuyse, et al., 2009; van Erp et al., 2015). Thus, even with the most careful clinical assessment, some signs of awareness can be missed because the clinical diagnosis relies on motor signs of awareness and language perception. Several standardized assessment tools based on behavioral observations have been developed. In a comprehensive evidence-based review of the psychometric properties of existing assessment scales, the Coma Recovery Scale-Revised (CRS-R; Giacino, Kalmar, & Whyte, 2004) was recommended with minor reservation, while the Sensory Modality Assessment Technique (SMART; Gill-Thwaites, 1997), Western Neuro Sensory Stimulation Profile (WNSSP; Ansell & Keenan, 1989), Sensory Stimulation Assessment Measure (SSAM; Rader & Ellis, 1994), Wessex Head Injury Matrix (WHIM; Shiel et al., 2000), and Disorders of Consciousness Scale (DOCS; Pape, Heinemann, Kelly, Hurder, & Lundgren, 2005) were recommended with moderate reservation (Seel et al., 2010). Moreover, the CRS-R is the only measure that incorporates the existing diagnostic criteria for coma, VS and MCS into the administration and scoring scheme (Schnakers, Edlow, Schiff, & Laureys, 2016). However, all standardized measures depend on the patient's ability to move and communicate. Thus, consciousness may be masked as a result of severe sensory and motor deficits (Majerus, Gill-Thwaites, Andrews, & Laureys, 2005), or because voluntary responses are highly inconsistent and easily exhausted. Giacino and colleagues (Giacino et al., 2009) have highlighted that there are multiple sources for misdiagnosis, as contributed by the examiner, the patient, and the environment. Examiner error may arise when diagnosis is not based on repeated examinations by well-trained professional healthcare staff. Source of variance may also be seen among the patients, such as fluctuations in arousal level, fatigue, subclinical seizure activity, pain, cortical sensory deficits, motor impairment, or cognitive disturbance. Environmental sources such as paralytic and sedating medications, poor positioning, and noisy environment, may also distort voluntary behavioral responses. All these issues may compromise the diagnostic validity of behavioral assessment. Emergence from MCS and recovery of consciousness has been defined by object manipulation and/or functional, accurate communication (Giacino, 2004; Giacino et al., 2002). Hence, patients have to be able to consistently express goal-directed, meaningful environmental interaction to be clinically categorized as emerged from MCS, but will often have severe cognitive deficits (Giacino, 2004). Thus, many of the above-mentioned confounding factors also may prevent detection of recovery of consciousness. In summary, clinical misdiagnosis is a continuing concern, potentially leading to serious consequences, such as unsatisfactory decisions related to pain treatment, the intensity and duration of rehabilitation services, and prognostic considerations, in the worst case with consequences for end-of-life decisions. Subsequently, there is an explicit need for motor-independent signs of awareness derived directly from brain signals.

Differential diagnosis

There are other conditions after brain injury characterized by behavioral unresponsiveness that must be differentiated from VS and MCS. The *locked-in syndrome* (LIS) is a condition marked by tetraplegia with near-normal to normal cognitive function and maintenance of consciousness (American Congress of Rehabilitation Medicine, 1995). A lesion involving the ventral pons causes this state. Because patients with LIS have spontaneous eyes opening, but are unable to speak or move the extremities, this state can be confused with VS (Giacino et al., 2009). *Akinetic mutism* is a condition most often caused by brain injury in bilateral medial frontal lobes and anterior cingulate cortex (Goldfine & Schiff, 2011). The condition is characterized by failure to follow commands, speak and engage in other goal-directed behavior due to severely diminished drive, rather than decreased arousal. Patients with akinetic mutism can be mute and behaviorally non-responsive when verbally prompted, with the risk of being interpreted as DoC (Giacino et al., 2014).

Recovery and treatment options in DoC

Recovery and prognosis in patients with DOC

Outcome studies relating to DoC concern rates of mortality, recovery of consciousness and long-term outcome. With regard to mortality in DoC, a five-year follow up study of patients who were either in VS or MCS (of mixed etiology) at admission into an intensive care unit found that the mortality rate was lower for patients admitted in a minimally conscious state (36%) compared with those admitted in a vegetative state (75%) (Luaute, Maucort-Boulch, Tell, Quelard, Sarraf, 2010). Mortality rates have also been found lower for patients in MCS with command-following at rehabilitation admission compared to those admitted in a VS or without command-following. (Greenwald et al., 2015). Expected survival increases with time in VS, where an expected survival of two to five years has been estimated for patients surviving one month in VS. For those surviving in VS at one year, if young, the mean survival has been estimated to 10.5 years, and for those in VS at four years, an expected mean of 12.2 further years has been estimated (Beaumont & Kenealy, 2005).

When estimating prognosis in DoC and recovery of consciousness, the level of consciousness and length of time post-injury are key predictors (Giacino et al., 2013). In prognostic studies, severe acquired brain injuries are often dichotomized into TBI versus non-traumatic brain injury (non-TBI), the latter including anoxic brain injury, stroke, and infectious, toxic, and metabolic disorders. It has been repeatedly demonstrated that the prognosis for recovery of consciousness is substantially better for victims of TBI than those with non-traumatic etiologies (Estraneo et al., 2010; Giacino et al., 2013; The Multi-Society Task Force on PVS, 1994). This is also reflected in the earlier mentioned practice guidelines published in 1995, which specified the probability for recovery of consciousness in VS to be considered as very poor at 12 months after TBI and at three months after non-TBI (The Quality Standards Subcommittee of the American Academy of Neurology, 1995). Importantly, when MCS is diagnosed during the acute stage, there is considerable variability in functional outcome after one year, where patients in MCS, as a group, may have a longer course of recovery and may achieve more favorable outcomes by one year post-injury, relative to patients in VS (Giacino, 2004). However, MCS may also represent a persistent outcome.

Recent studies indicate that the prospects for late recovery are however, better than previously thought, at least for victims of TBI (Nakase-Richardson et al., 2012). Luauté and colleagues

conducted up to five-year follow-up of patients of mixed etiologies who were either in VS or MCS at least one year after the brain insult. They reported that a third of the patients with MCS emerged from MCS with severe disabilities more than one year post-injury, but none of the patients in VS improved during the follow-up period (Luaute et al., 2010). Lammi and colleagues also conducted long-term follow-up two to five years post-injury in patients in MCS for at least one month following TBI. They found large heterogeneity in outcome, with 15% of their sample having partial disability or better functioning measured with the Disability Rating Scale (DRS; Rappaport, Hall, Hopkins, Belleza, & Cope, 1982) at follow-up, while 20% fell in the extremely severe to vegetative category (Lammi, Smith, Tate, & Taylor, 2005).

Treatment options for patients in DoC

Therapeutic options in VS and MCS are limited, and there is still no treatment strategy proven to be efficient in alleviating DoC. Medical care is primarily aimed towards maintaining body functions and preventing, as well as treating, medical complications, which patients with DoC are prone to suffer from, along with facilitating cognitive improvement and communication abilities (Giacino et al., 2013; Whyte, Nordenbo, et al., 2013). It has been underscored that many of these complications require brain injury expertise for optimal management (Whyte, Nordenbo, et al., 2013). It is therefore critical that patients with DoC are provided with medical assessments within specialized health care institutions.

Sensory stimulation, pharmacological interventions and brain stimulation treatment While the evidence for effectiveness of structured sensory stimulation has yet to be demonstrated (Di, 2012; Giacino et al., 2013), there is some evidence for the effect of pharmacological interventions. Two medications that have been demonstrated effective in randomized clinical trials with regard to improving behavioral responsiveness in patients with DoC, are amantadine and zolpidem. Amantadine, a dopamine agonist, has proved effective in accelerating the pace of recovery in patients with posttraumatic DoC, in a large wellcontrolled multi-center study (Giacino et al., 2012). The study included 184 patients between four and 16 weeks after TBI, who received either amantadine or placebo for four weeks, followed by a two-week washout. The rate of recovery was significantly faster in the amantadine group in patients whom were in both VS and MCS at baseline. Although the functional gains were maintained after the treatment period, the rate of recovery slowed substantially, and at six weeks follow-up assessment the group differences were indistinguishable. The long-term effects of amantadine are however, not well documented. Zolpidem, a GABA agonist, has been recognized to induce paradoxical arousal-promoting effects in a minority of patients of DoC. In a placebo-controlled, double-blind, crossover trial of 15 patients with DoC (12 VS and 3 MCS), one single patient showed marked improvement in level of consciousness, indicating low response rates (Whyte & Myers, 2009). The authors have hypothesized that the paradoxical effect of zolpidem acts to inhibit neural networks that are already strongly inhibited due to damage.

Systematic assessment of pain and nociception in non-communicative patients with DOC constitutes an additional challenge for clinicians. To date, no fully validated assessment scale exists. However, a specific tool for assessing nociception in patients with DoC has recently been developed; the Nociception Coma Scale-Revised (NCS-R; Chatelle, Majerus, Whyte, Laureys, & Schnakers, 2012; Schnakers et al., 2010). Sunnaas Rehabilitation Hospital is currently involved in a multicenter study investigating the validity of the NCS-R. With regard to pain management and medication, the pros and cons of the use of analgesia in those who are severely brain damaged, and are unable to communicate possible perception of pain, are debated. Systematic use of narcotic analgesics in patients with DoC can lead to sedation and thereby conceal signs of consciousness. While some clinicians recommend that pain treatment be given to all patients in vegetative state or MCS (Schnakers & Zasler, 2007), others propose that special precaution needs to be taken especially with regard to patients in MCS, as they may have the capacity for subjective pain perception (Giacino et al., 2013).

At an experimental level, there has also been a growing interest in the use of invasive and non-invasive brain stimulation techniques to restore cognitive and behavioral functions in patients with prolonged DoC, such as deep brain stimulation of the thalamus. Schiff et al., (2007) reported behavioral improvement in a patient with prolonged MCS who was treated with deep brain stimulation of the thalamic intralaminar nuclei. The patient showed treatment-related improvements of increased arousal, consistency in functional motor movements, behavioral persistence and oral feeding, leading the authors to propose a possible explanation in restored activation of frontal cortical and basal ganglia systems connected to the thalamus (Schiff et al., 2007). Non-invasive transcranial direct current stimulation (tDCS) has also been applied to patients in MCS. Thibaut et al. (2014) investigated the use of tDCS in 55 patients with DoC, with increased treatment-related improvements in 43% of patients in MCS.

However, they did not find that functional gains were maintained at one-year follow-up (Thibaut, Bruno, Ledoux, Demertzi, & Laureys, 2014).

Prognostic challenges in severe TBI

The initial severity of TBI is commonly graded by assessment of the Glasgow Coma Scale (GCS; Teasdale & Jennett, 1974), and a GCS score of 3–8 represents severe TBI, while a score of 9–12 represents moderate TBI, and a score of 13-15 mild TBI (Chesnut, 1997). However, obtaining accurate scores for the GCS can be difficult, as scores might be obscured in the acute settings due to intoxication, medical sedation or paralysis (Andelic et al., 2010). The use of CT scan as an objective measure of the structural brain injury can assist in discriminating less severe versus more severe TBI using the Marshall Classification (Marshall et al., 1992).

TBI is a major global public health problem, and a leading cause of death and disability. In the United States, it is estimated that least at 1.7 million people sustain a TBI each year, and that there are more than 50 000 annual TBI-induced deaths (Coronado et al., 2011; Faul & Coronado, 2015). Incidence of TBI in Europe over the last 20 years has been reviewed by Tagliaferri and colleagues (Tagliaferri, Compagnone, Korsic, Servadei, & Kraus, 2006), summarizing that there is a large variation in estimated incidence of severe TBI across studies, from 7.1-20.0 per 100 000. In a population-based study in Norway, the incidence of severe TBI, defined by a GCS of 3–8 (Teasdale & Jennett, 1974), was estimated to be 5.2 per 100 000 in 2009 and 4.1 per 100 000 in 2010. Eighty patients (29%) died after hospital admission in this study, and the majority died within 48 hours after admission (Andelic, et al., 2012). The in-hospital fatality rate in this study is in accordance with earlier fatality reports (Maegele et al., 2007; Walder et al., 2013).

The trajectories and the degree of functional and cognitive improvements after severe TBI are highly variable (Andelic et al., 2009; Anke et al., 2015; Jourdan et al., 2016; Ponsford, Draper, & Schonberger, 2008; Sigurdardottir et al., 2015). Cognitive deficits are common sequelae after moderate to severe TBI (Dikmen et al., 2009), especially affecting executive functions, processing speed and memory functions (Sigurdardottir et al., 2015), along with substantial long-lasting impaired overall health (Andelic et al., 2009; Andelic et al., 2010; Søberg et al., 2013), and difficulties with community integration and work (Dahm & Ponsford, 2015; Livingston, Tripp, Biggs, & Lavery, 2009). Accurate prognostic estimation in

the early phase after a severe brain injury is still a major clinical challenge. Will the patient survive the initial phase in the neurointensive care unit (ICU)? Which patients have the probability of a good outcome and who will remain in a prolonged state of DoC? Who might profit from intensive rehabilitation efforts? These are major clinical issues that health professionals need to address when dealing with patients suffering from the most severe TBI.

At present, predicting survival, outcome and long-term cognitive deficits in individual patients with severe TBI based on clinical assessment is very difficult. Major efforts have been put into developing prognostic models based on clinical and laboratory parameters from the acute phase to aid in outcome prediction after TBI. Both the IMPACT (International-Mission-For-Prognosis-And-Clinical-Trial) and CRASH (Corticosteroid-Randomisation-After-Significant-Head injury) models are based on large, prospective patient cohorts, where high age, low GCS, absent pupillary reactivity has been associated with poor outcome or death. In addition, certain CT characteristics have been strongly associated with outcome, in particular injuries of the ambient cisterns and have been highlighted (Perel et al., 2008; Jacobs et al., 2013; Steverberg et al., 2008). These models provide predictive algorithms providing an objective measure of the likely outcome at an individual patient level early in the course of their disease. However, the psychometric properties of these methods and their limitations in mainly focusing on predicting mortality have been criticized (Castano-Leon et al., 2016; Jacobs et al., 2013; Sandsmark, 2016). Furthermore, the fact that they do not take newer advancements in critical care management into consideration causes overestimation of the risk of mortality or unfavorable outcome (Honeybul, Ho, Lind, & Gillett, 2014; Olivecrona & Koskinen, 2012; Olivecrona & Olivecrona, 2013). The CRASH model has also been found to overestimate mortality and unfavorable outcome in elderly people following severe TBI (Røe et al., 2013). A Canadian study found that 70% of the deaths reported in six level I trauma centers were attributable to withdrawal of life-sustaining therapy, half of which occurred within the first 72 hours of traumatic injury (Turgeon et al., 2011). However, it is not known to what degree decisions to withdraw life-sustaining therapy in the acute phase accurately meet the true mortality rates or very unfortunate outcomes, such as persistent VS, in this patient group.

The diagnostic and prognostic utility of modern neuroscientific methods

Modern techniques for functional imaging of the living human brain represent a paradigm shift in the potential to study ongoing brain functioning, which can now be studied with

neuroscientific techniques, such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI) diffusion tensor imaging (DTI) and electrophysiological techniques (Laureys & Schiff, 2012). These scientific and technological advances have allowed both structural and functional studies of the living brain, enabling online monitoring of mental processes, including the neural correlates of human behavior, included consciousness. In a seminal paper published in 2006, Owen and colleagues described a young female patient behaviorally diagnosed as being in VS, who was scanned with fMRI while instructed to imagine playing tennis and to navigate through her home (Owen et al., 2006). The brain activation patterns appeared very similar to those observed in healthy controls, leading the authors to conclude that the patient was responding to command and therefore retained a level of consciousness and cognitive capacity that was not behaviorally detectable. This fascinating case was heavily debated after it's publication, and it has been suggested that she was probably in a state of transition to MCS, as behavioral changes were reported a few months later (Fins, 2008). In relation to diagnosis of patients with DoC, the promise of modern neuroscientific methodology lies in the fact that indices of cognitive processing can be derived in the absence of behavioral requirements when applying experimental paradigms encompassing active tasks requiring mental processing. It has also been advocated that modern neuroscientific methods in combination with active tasks that require effortful mental processing also show promise in adding prognostic information (Edlow et al., 2013; Vogel et al., 2013).

Event Related Potentials (ERPs)

Electroencephalography (EEG) measures the electrical activity from groups of cortical neurons recorded from scalp electrodes. EEG has the advantage of being non-invasive, can be applied repeatedly at bedside, as well as being much less expensive than fMRI. While fMRI has the benefit of high spatial resolution, the temporal resolution is low, requires high technical skills, and is usually not accessible in rehabilitation facilities (Cruse et al., 2011; Duncan et al., 2009; Reinvang, 1999). ERPs are extracted from continuous EEG while participants are exposed to repeated stimulus presentations in cognitive tasks. ERPs are recorded at individual electrodes of varying numbers, and commonly placed in accordance to the international 10-20 system (Klem, Luders, Jasper, & Elger, 1999). See figure 3. Experiments with intracranial recordings are also performed, but are far more invasive (Flinker, Chang, Barbaro, Berger, & Knight, 2011; Ritaccio et al., 2012). Signal averaging is used to eliminate the background EEG activity, and thus derive an averaged measure of

stimulus-related processing (Reinvang, 1999). ERPs represent small perturbations of synchronous electrical activity in neuron ensembles, signaling time-locked EEG activity elicited by internal or external events. Thus, repeating specific stimuli multiple times and averaging together the corresponding time-locked EEG activity, amplifies the stimulus-related response, while irrelevant background activity is cancelled out. Thus, ERPs provide a neurophysiological correlate of cognitive processing at the millisecond level (Picton, Lins, & Scherg, 1995), from early components, i.e. the N1 component reflecting primarily auditory sensory processing, to later and waveforms, such as the P3 reflecting more complex cognitive processes (Soltani & Knight, 2000). Early components are largely considered to be determined by physical stimulus characteristics and have traditionally been termed "endogenous" components, while cognitively mediated components have been termed "exogenous" (Picton, Lins, & Scherg, 1995). Some highly endogenous and short-latency evoked potentials include brainstem auditory evoked potentials (BAEP) and somatosensory evoked potentials (SEP). These evoked potentials are elicited by stimulation of specific sensory pathways and can be used to assess the integrity of auditory (BAEP) or somatosensory (SEP) pathways (Boly, Gosseries, Massimini & Rosanova, 2016; Guerit et al., 2009; Luck, 2014b).

ERP waveforms are typically described by referring to the polarity of the curve, that is, positive (P) or negative (N), sequential order of their temporal occurrence (P1, P2, N1, N2, etc.) or to the time point, measured in milliseconds (ms), at which the maximum amplitude of the waveform is observed, i.e. N100 or P300 (Reinvang, 1999). Hence, ERPs can provide valuable information about the timing, and if applying high-density EEG, also cortical distribution, of neuro-electrical activity in the brain, as this is generated by mental activity. Artifacts, such as motor activity, may decrease the signal-to-noise ratio of the averaged ERP waveform and must be properly dealt with by eliminating or correcting procedures. One way to reject non-brain activity, such as eye-blink artifacts, is by offline processing through independent component analysis (ICA), and hereby separating EEG activity into linearly independent components (Delorme & Makeig, 2004). This procedure classifiers the EEG activity and components can by visual inspection or by automated classifiers be recognized as "real" brain activity or artifacts, such as eye blinks or muscle activity.



Figure 3: Adapted illustration of EEG recording for the ERP technique. Raw EEG is recorded with scalp electrodes embedded in an electrode cap, placed according to the International 10/20 System. This system names each electrode site using letters to indicate the general brain region (F for frontal, C for central, P for parietal) and a number for indicating the hemisphere (odd for left and even for right), as well as distance from the midline (higher numbers indicate larger distance). EEG activity from each electrode is amplified and converted into digital form stored on a computer. Stimuli presented are marked as event-codes along with the EEG data. The ERPs are extracted from averaging over repeated stimulus presentation (Luck, 2014a).

Some of the most common ERP components associated with automatic and controlled attention relevant for this thesis, are here highlighted and described according to their temporal order:

The auditory N1 and the mismatch-negativity

The N1 component typically occurs around 100 ms after auditory stimulus onset, and is thought to reflect early auditory sensory processing primarily generated from the auditory sensory cortex. The mismatch-negativity (MMN) is an attention-independent, change-specific component of the auditory ERP (Naatanen, 1995; Naatanen, Paavilainen, Rinne, & Alho, 2007). Paradigms designed to elicit the MMN usually involve a large number of repeated stimulus presentations (standards) with a small proportion of deviants, defined by physical parameters, such as variations in duration, intensity, or frequency (Reinvang, 1999). The MMN is defined as the difference waveform elicited from deviant and standard stimuli. Hence, it represents an automatic detection of a stimuli-difference in the sensory system, typically peaking at 120-200 ms (depending on stimuli characteristics) after a detectable change in the stimulation, and is present even if subjects are not aware of the stimuli changes (Morlet & Fischer, 2014; Naatanen & Picton, 1987). 30

The P3 component - ERP in detecting consciousness

The well-established P3 component has attracted particular interest in the DoC population, as it reflects allocation of attentional and memory resources (Polich, 2007; Soltani & Knight, 2000). In healthy persons, the P3 amplitude derived from an auditory odd-ball paradigm typically peaks between 300 and 600 ms post stimulus (Soltani & Knight, 2000), but P3 responses in brain injured patients often show prolonged latencies and attenuated amplitudes relative to healthy subjects (Duncan et al., 2009; Duncan, Summers, Perla, Coburn, & Mirsky, 2011; Solbakk, Reinvang, & Andersson, 2002; Wijnen, Eilander, de Gelder, & van Boxtel, 2014). The P3 component is most prominent in tasks that subjects are attending to, and the most frequently applied paradigm for eliciting a P3 response is the oddball paradigm, wherein subjects detect and respond to occasional target stimuli interspersed between frequently occurring standard stimuli (Picton, 1992; Soltani & Knight, 2000). In auditory oddball paradigms, the scalp distribution of the P3 is widespread and typically has a maximum peak over the mid-parietal region. The P3 component is also larger when stimuli are more improbable (Picton, 1992). It has also been proposed that passive stimulus processing generally produces smaller P3 amplitudes than active tasks, because stimulus and non-task events engage attentional resources to reduce amplitude (Polich, 2007).

Recent studies have investigated cognitive ERPs as a marker of consciousness in patients with DoC, where the P3 component elicited in tasks requiring cognitive effort has been widely investigated (Gosseries, Zasler, et al., 2014; Laureys & Schiff, 2012; Noirhomme, Brecheisen, Lesenfants, Antonopoulos, & Laureys, 2015; Peterson, Cruse, Naci, Weijer, & Owen, 2015). In ERP studies, it is recommended that ERP-tasks should be adapted to the subjects studied (Picton et al., 2000). Hence, in ERP experiments including patients with severe brain injuries, it has been shown that the probability of eliciting electrophysiological responses increases with the use of salient self-referential stimuli, such as exposure to the subject's own face or name (SON; Laureys, Perrin, & Bredart, 2007). The advantage of such electrophysiological methods lies in the fact that indices of cognitive processing can be derived in the absence of behavioral requirements. However, inference of consciousness based on passive ERP paradigms is insufficient, as passive tasks without demand of volitional mental effort can elicit a P3 response in comatose or VS patients (Fischer, Luaute, & Morlet, 2010b; Perrin et al., 2006), and in healthy subjects under anesthesia (Fowler & Mitchell,

1997). Hence, it is necessary to include experimental paradigms encompassing active tasks requiring mental processing.

Schnakers and colleagues presented a list of eight randomized names, including SON (Schnakers et al., 2008). When instructed to actively count a target name (either SON or an unfamiliar name (UN)), the MCS, but not the VS group, showed an increase in P3 amplitude. The study reported that 9/14 individual patients in MCS had enhanced P3 amplitudes in at least one out of two active counting conditions. Also, covert command-following was detected in two patients in MCS with absence of externally observable signs of commandfollowing. In a more recent study, the Schnakers et al. (2015) experimental paradigm was developed into a single-stimuli design, presenting SON in a passive listening condition along with an active condition, instructing patients to listen for a change of pitch in the voice saying their name. They found that 5/8 patients in MCS+ and 3/8 patients in MCS- versus only 1/10 VS patients displayed enhanced P3 amplitude in the active versus passive condition. Other studies using active ERP paradigms have also demonstrated signs of covert mental effort in DoC at a single patient level, and many with ERP paradigms encompassing active counting of auditory stimuli. Yet, the choice of auditory stimuli and experimental designs has been heterogeneous, including counting of SON (Risetti et al., 2013), the word YES or NO (Chennu et al., 2013), or a global deviant sound (Bekinschtein et al., 2009; Faugeras et al., 2011; Faugeras et al., 2012).

The extent to which a combination of experimental paradigms with active conditions during electrophysiological recordings can complement standardized neurobehavioral assessment, or which type of experimental procedure or neurophysiological measure are the most robust and best suited, is still not well described. Both are paramount in order to establish the diagnostic value of the methods in clinical practice, where correct assessment of the level of consciousness in patients with DoC is crucial, but challenging.

Prognostic usefulness of electrophysiology in severe brain injury

Early and reliable prognostication of patients with severe acquired brain injuries is very challenging, but essential for treatment planning. Electrophysiological techniques, such as evoked potentials, have shown some promise in aiding prognostic evaluations in the early phase. Specifically, SEPs have demonstrated high specificity in predicting poor outcome in

anoxic coma (Carter & Butt, 2001, 2005; Guerit, 2010; Robinson, Micklesen, Tirschwell & Lew, 2003). In a meta-study of the prognostic value of SEP in brain injury of mixed etiologies, 44 studies including either normal or bilaterally absent SEP were included, and outcomes were dichotomized into favorable (normal or moderate disability based on the Glasgow Outcome Scale (GOS; Jennett & Bond, 1975), or unfavorable (the GOS categories severe disability, vegetative or death). Of 777 patients with bilateral absent SEPs, only 12 had a favorable outcome, providing a specificity rate of 98.7% given bilaterally absent SEPs (Carter & Butt, 2001). Another large review by Robinson and colleagues (2003) investigated the prognostic value of SEP for awakening from coma in 41 studies including 2701 comatose patients of mixed etiologies (Robinson et al., 2003). Outcomes were categorized as persistent vegetative state or death versus awakening. The review showed that of all 1136 included patients with anoxic injury, 336 had bilateral absent SEP, of which all had unfavorable outcome. Of the anoxic patients with present, but abnormal SEP (310 patients), only 22% had a favorable outcome with return to consciousness. Looking at a subset of 232 patients with TBI for whom SEPs were absent bilaterally, only 5% of the group awakened. Seventy percent of the TBI patients presenting present, but abnormal SEP awakened, contrarily to patients with anoxic injuries. Also, the systematic review showed an overall 28% presence of normal SEP in TBI-induced coma, where normal SEP had a sensitivity rate of 57% for predicting good recovery measured with GOS (Robinson et al., 2003). However, these studies do not take into account serial SEP recordings and the possibility of sub-acute normalization of SEPs, they lack systematic investigation of the quality of present SEPs through an established grading system, and are moreover restricted by dichotomous and coarse outcome measures. In addition, the studies used very early follow-up time points, as early as one month post injury (Carter & Butt, 2001; Robinson et al., 2003). Of note, the prognostic accuracy of the absence of SEPs has been shown to be lower if severe brain injury is caused by TBI, as recovery of bilateral absent SEP followed by favorable outcome may occur more often than after other etiologies, such as anoxia (Folmer, Billings, Diedesch-Rouse, Gallun & Lew, 2011; Robinson et al., 2003; Rothstein, 2000; Schorl, Valerius-Kukula & Kemmer, 2014). Hence, the origin of the condition which causes coma affects the predictive value of short-latency EPs, where normal SEP constitutes a favorable sign in TBI, and bilateral absence of SEP is a strong indicator of unfavorable outcome in anoxia (Guerit, 2010; Mazzini, 2004). BAEPs have been less extensively studied in TBI, but it has been summarized that absence of wave V is

correlated with poor outcome in posttraumatic coma, as long as wave I, indicating integrity of the auditory pathway, is present (Wang, Young & Connolly, 2004).

One meta-analysis concluded that the presence of either the N1 component, MMN, and the P3 were all highly significant predictors of awakening, but they found the P3 and MMN to be better predictors than the N1 for awakening from coma. The authors also found that their data are in line with the literature indicating that traumatic and post-operative (such as tumor or vascular neurosurgery) etiologies have the best chance of awakening, whereas the lowest rate of awakening is seen for anoxia and metabolic encephalopathy (Daltrozzo, Wioland, Mutschler & Kotchoubey, 2007). However, no conclusions on the prognosis can be drawn from the absence of a P3, because patients without a P3 during coma have been found to have good or bad outcomes alike (Daltrozzo et al., 2007). There is however, scarce knowledge of the prognostic utility of ERPs beyond mere awakening from coma and detection of consciousness (Lew, Poole, Castaneda, Salerno & Gray, 2006; Mazzini, 2004; Wang et al., 2004).

Main research objectives

Accurate diagnosis of patients with DoC with regard to level of consciousness is still a major clinical challenge. In addition, precise prognostication after severe TBI is very challenging in the early phase post-injury. Modern neuroimaging and neurophysiological techniques have shown some diagnostic promise in patients with DoC after acquired brain injury, with the advantage of circumventing the need for motoric responses. Herein, studies have shown that covert electrophysiological signs of consciousness can be detected in patients with DoC. However, the precise clinical diagnostic utility of electrophysiological recordings in combination with active experimental paradigms is yet not well described. Moreover, neurophysiological methods have demonstrated prognostic utility in patients with severe acquired brain injuries, where high specificity of the two ERP components MMN and P3 in predicting awakening from coma after acquired brain injury, has been demonstrated. However, beyond mere awakening from coma, there is a lack of knowledge regarding the utility of cognitive ERPs in predicting long-term functional and cognitive outcome.

The main research objectives of this PhD project were:

- To investigate the diagnostic utility of cognitive ERPs in patients with DoC following acquired brain injury. Herein, a main objective was to study how well two different ERP-tasks that both require active mental processing can detect neurophysiological signs of command-following in a group of both healthy controls and patients in MCS. The objective was also to investigate the tasks ability to detect covert neurophysiological signs of command-following in patients in MCS with no behavioral signs of such cognitive capacity. Finally, the study aimed to systematically investigate the body of existing literature, in order to estimate the clinical diagnostic usefulness of neurophysiological measures in patients with DoC.
- 2. To explore presence and normalization of cognitive ERPs recorded repeatedly in the sub-acute phase after severe TBI, and to investigate ERPs' association with outcome. Herein, the main objective was to investigate the P3 component elicited in an active task. A further objective was to compare presence of P3-difference between an active and a passive task at an individual patient level across repeated recordings, as well as normalization of the P3 elicited in the active task. A further aim was to explore the association between the P3-response to the active task and functional and cognitive outcome six months post-injury.

The three main hypothesis in the study were:

Cognitive ERPs will prove diagnostic utility in patients with DoC following acquired brain injury. Furthermore, ERPs can inform on residual cognitive capacity in the early phase following severe TBI, and sub-acutely recorded ERPs are associated with functional and cognitive outcome.

Methods

Design

Paper I: Paper I used a within-subject design. This study included both healthy subjects and a convenience sample of patients with stable DoC.

Paper II: The design in paper II was a systematic literature review, which included empirical studies applying electrophysiological methods in combination with active cognitive tasks to detect mental processing in patients with DoC.

Paper III: The experiment in paper III constituted a longitudinal within-subject design, which included a consecutive sample of patients with severe TBI.

Participants

Paper I: Twenty-two healthy controls aged 18-65 years were enrolled in the study. All were native Norwegian speakers with no previous history of brain injury, neurological or psychiatric illness, premorbid hearing impairments, or subjective experience of cognitive impairment. Health personnel at Sunnaas Rehabilitation Hospital were recruited as healthy controls. Twenty-two patients were enrolled from the Brain Injury Unit at Sunnaas Rehabilitation Hospital in Oslo, Norway, and two patients from St. Olavs Hospital in Trondheim. All were above 18 years of age and were fluent Norwegian-speaking prior to their injury. All were in a stable phase with DoC after severe acquired brain injury of mixed etiology, and the ERP recordings were performed at least 90 days post-injury. Patients were assessed with the CRS-R and met the diagnostic criteria for MCS (Giacino et al., 2002). All patients had a documented presence of auditory startle (i.e. CRS-R auditory subscale score \geq 1), or a detectable auditory N1 ERP component, indicating intact hearing. Two controls and four patients were excluded due to low quality EEG recordings (i.e. ocular, muscle, and/or noise artifacts that could not be adequately corrected). Hence, 20 controls (mean age = 38, range 25-61 years, 10 males) and 20 patients (mean age = 40, range 19-66 years; 11 males) were included in the final ERP analysis.

Paper III: The study included 19 consecutively included adult patients admitted to the intensive care unit at the level 1 trauma center for the southeast of Norway (Oslo University Hospital; OUH) from September 2013 to June 2015. For inclusion, patients needed to be adults with age between 18 and 65, residents of the southeast region of Norway, fluent Norwegian speakers prior to their injury, admitted with severe TBI defined according to the International Classification of Diseases, Tenth Revision, criteria (S06.1-S06.9: intracranial brain injury presenting as traumatic cortical edema; focal or diffuse TBI; epidural, subdural, or subarachnoid hemorrhage, and/or other specified or unspecified intracranial injury) within 24 hours of injury, and had GCS between 3 and 8 over the first 24 hours following injury. In order to recruit the most severe end of the severe TBI population, inclusion criteria required that they had been in need of at least five days of neurointensive care. Exclusion criteria were severe comorbidities such as progressive neurological disorders, severe psychiatric and substance abuse disorders in need of treatment, or treatment with hemicraniectomy. Patients
were excluded if they had a bilaterally absent brainstem auditory evoked potentials (BAEP) along with absent auditory N1 ERP component, indicating primary sensory processing disorders. Five patients were excluded from the initial sample due to lack of cooperation, low EEG-quality or medical complications. Therefore, the remaining sample of 14 patients (mean age =38.2 (SD=14.7); 8 males) completed the experimental procedure, including follow-up. All in all, 76 patients with GCS lower than 9 were evaluated for study inclusion, but not found eligible during the recruitment period. Two patients were not included due to lack of consent from next of kin, seven died during the initial phase, ten had hemicraniectomy, eleven did not have a Norwegian residency or were not prior fluent Norwegian speakers, and the rest were not eligible due to high age, severe premorbid psychiatric or substance abuse disorders, or had early transfer to ICU at a local hospital.

Procedures

ERP-experimental paradigm and procedures

Detailed descriptions of the experimental paradigms can be found in the method section in papers I and III. At the start of the study, there was little knowledge available regarding robustness of different active ERP conditions. Also, most ERP-studies had previously been presented at a group basis of DoC or single patients (Bekinschtein et al., 2009; Schnakers et al., 2009; Schnakers et al., 2008). The ERP design chosen for the PhD study was established in close collaboration with co-supervisor of the project, Caroline Schnakers, who had previously published two papers applying an ERP-design encompassing both an active and a passive condition using SON and UN. Hence, the ERP-design was an elaboration of Schnakers previously published design, including two different active conditions, both compared with a passive listening task, and exposed to the subjects in a fixed hierarchical order. The same experimental ERP-paradigm was conducted in both the diagnostic study with patients in a stable DoC (data published in paper I) and the longitudinal study with repeated EEG recordings sub-acutely in patients with severe TBI (paper III).

The ERP-paradigm included: (1) active listening to change in pitch to the subject's own first name (SON) repeated 100 times and (2) active counting of SON (SON: 50 times), randomly interspersed between an unfamiliar name (UN: 50 times), both contrasted to a passive condition, see figure 4. The Single SON Passive condition was introduced first, with the instruction to do nothing but to stay awake. Thereafter, the subjects were presented with the

Single SON Active condition, with the instruction to listen very carefully for a change in the pitch of the voice saying their name. There was no actual change in the voice, rendering the physical stimulus characteristics identical, and the demanded level of mental effort was the only difference between conditions. Task 2 included a two-stimuli SON/UN Passive and Active condition. In the passive condition, the subjects were instructed to do nothing but to stay awake. In the active condition, subjects were instructed to count the number of times they heard SON. All four conditions were presented in the same hierarchical order (each condition containing four sets of consecutive blocks of 25 stimuli, 100 in total). In addition, the design included a MMN-paradigm. This paradigm contained standard and deviant tones, which varied in duration (75 and 25 ms). A total of 1500 stimuli were presented, with a 400 ms inter-stimulus interval and a 15 % deviant probability. However, the MMN experiment does not form part of this thesis, but results will be prepared for future publications.



Figure 4: ERP-paradigm encompassing two different tasks, both encompassing active and passive conditions.

All EEG recordings were performed while participants were in a wakeful state. For the patients, a short break, and if needed, brief auditory or deep pressure stimulation according to CRS-R protocol were applied between conditions in order to ensure adequate arousal levels. CRS-R was applied for behavioral assessment of level of consciousness and conducted by an experienced rater on the day of EEG recordings. In paper III, EEG-recordings were conducted repeatedly biweekly at three time-points sub-acutely in a consecutive sample of patients with severe TBI. The same ERP paradigm consisting of two tasks, illustrated in figure 4, was applied in both paper I and III.

EEG-recordings

The ERP-data presented in paper I and III were all acquired using a 32-electrode cap (Quikcap; Compumedics Neuroscan) connected to a portable digital NuAmp EEG amplifier (Compumedics Neuroscan), see figure 4. Detailed information about the EEG recordings, offline processing of data, and strategies for ERP-analysis can be found in the method section of paper I and paper III.

Methods for systematic review

The primary objective for the systematic review (paper II) was phrased using the PICOapproach (patient problem, intervention, comparison and outcome; (Schardt, Adams, Owens, Keitz, & Fontelo, 2007)): In patients with DoC (P), to what extent can electrophysiological techniques used in combination with active experimental paradigms (I) supplement standard behavioral measures (C) in detecting voluntary cognitive processing (O)? Furthermore, recommendations for systematic reviews were followed (Deeks, 2013; Kable, Pich, & Maslin-Prothero, 2012; Moher et al., 2015). To ensure transparent and complete reporting of the review, the PRISMA (Preferred reporting items for systematic review and meta-analysis) guidelines were followed (Liberati et al., 2009; Moher, Liberati, Tetzlaff, Altman, & Group, 2009; Shamseer et al., 2015). Quality appraisal of the retrieved literature was conducted using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2). This is a tool for assessment of the risk of bias of included studies in systematic reviews of diagnostic accuracy. It comprises 4 domains; patient selection, index test, reference standard, and flow and timing. Each domain was assessed in terms of risk of bias, and the first three domains were also assessed in terms of concerns regarding applicability. In line with the recommendations, the QUADAS-2 signaling questions were tailored to this specific review (Whiting et al., 2011) and guidelines on how to assess the signaling review-specific question were developed (for details, see supplementary materials in paper II).

Neuropsychological test measures and questionnaires for functional outcome

The prognostic study (paper III) included follow-up of patients with severe TBI at six months post-injury. Outcome measures included neuropsychological examination and global functional outcome classification with the Glasgow Outcome Scale- Extended (GOSE; Wilson, Pettigrew, & Teasdale, 1998). The following neuropsychological measures were applied: Intelligence coefficient (IQ) based on all four sub-tests of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), verbal memory and learning (Hopkins Verbal

Learning Test—Revised (Brandt, 2001), attentional set-shifting (Letter- Number Switching from the Trail Making Test (TMT, condition 4), Delis-Kaplan Executive Function System (Delis, 2001), inhibition and switching (Color-Word Interference Test (CWIT 3 and 4 from (D-KEFS)), and working memory (Digit Span backwards) from the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV; Wechsler, 2008). One patient did not complete neuropsychological testing due to severe cognitive deficit and post-traumatic confusion at follow-up.

Statistical analysis

In paper I, repeated measures analysis of variance (ANOVAs) was used to examine differences in mean or peak amplitude between stimulus types or conditions in the healthy control group, using SPSS version 22 for Macintosh (SPSS, Inc., Chicago, IL). SON versus UN and active versus passive was contrasted, with stimulus type (SON-UN) or condition (passive-active) as within-subject factors, and midline electrode location (Fz, Cz and Pz) as the second within-subject factor. Extreme values were identified using boxplots. Analyses including extreme values were repeated without these, and any changes in results were reported. Greenhouse-Geisser epsilon corrected p-values were reported for computations involving more than two levels of a repeated measures factor. When indicated by the ANOVA, post hoc tests with Bonferroni correction were employed. Partial eta squared (partial η^2) was used to calculate the sample effect size based on within-subjects factor variability. To investigate if each visually identified responder, both healthy controls and patients, could be confirmed statistically, an unpaired t-test was performed in the EEGLAB STUDY-function (Delorme & Makeig, 2004). Amplitude differences between passive and active conditions were tested at an individual level on a trial-by-trial basis for each sampling point, with Bonferroni correction for multiple comparisons. Rate of responders is described by actual numbers of subjects, percentage and by 95% Confidence Intervals (CI). Statistical significance was set to p<.05. Sensitivity and specificity of the ERP-tasks were calculated with CRS-R as the reference standard and MCS- as the disorder of interest.

In **paper II**, individual responder rates were described with actual numbers of subjects and percentage per study, meaning subjects showing signs of active mental effort during electrophysiological assessment, both in healthy subjects and patients with DoC. Patients who displayed unequivocal behavioral signs of command-following were classified as MCS+,

while patients with no reproducible behavioral response to command were classified as MCS-, in accordance with the definition provided by Bruno et al. (2012). Sensitivity and specificity were computed using data from the published articles and calculated with 95% CI per study, with the behavioral assessment as the reference standard and VS and MCS- as the disorder of interest. Sensitivity was understood as the ability of the electrophysiological assessment to detect command-following in patients behaviorally classified as MCS+. Specificity was understood as the ability of electrophysiological techniques to confirm the behaviorally based VS or MCS- diagnosis, by the lack of electrophysiological signs of command-following. Sensitivity and specificity rates were calculated according to the efficient-score method (Newcombe, 1998) (http://vassarstats.net/index.html).

In **paper III**, Firstly, P3 to SON in the active task was identified by visual inspection at an individual level in each recording. In cases where a P3 to SON was established, P3-amplitude differences in the passive versus the active condition to SON in T1, T2 and T3 were investigated with two-tailed paired t-tests on a trial-by-trial basis in each individual for each sampling point (in the individual P3 time-window to SON) at the midline electrodes Fz, Cz and Pz in the EEGLAB study function. Signs of normalization of the P3 elicited in the active task, that is, a development towards a clearly identifiable P3 component with increasing amplitudes across the 3 EEG-recordings, was explored by visual inspection, resulting in a group of 6 patients (patient 1, 4, 7, 8, 10, 12) whom displayed normalization, and a remaining group of 8 without detectable normalization. Normalization was then primarily analyzed as amplitude change over time for each condition, comparing peak P3-amplitudes at each midline electrode between T1 and T2, T2 and T3, and T1 and T3 in each group and experimental condition, using paired-samples t-tests. Secondarily, changes in amplitude difference was set to p < .05.

The relationship between the sub-acutely recorded P3 to SON in the active task and outcome at six months was examined with Pearson's correlations, including the following sub-set of outcome measures; functional outcome (GOSE), verbal learning (HVLT-R, total words learned), working memory (Digit Span backwards), attentional set-shifting (TMT) and inhibition and switching (CWIT 3 and 4). The effect of GCS on these associations was examined in partial correlations where acute GCS was controlled for. Analyses involving

neuropsychological variables were conducted on raw scores. Normality distribution was investigated with the Shapiro-Wilk's test (p < .05), and in cases of violation, analyses were repeated with non-parametric tests, with any subsequent changes in results being reported. *P*-values $\leq .05$ were considered statistically significant. Effect size was reported with *r* for correlations and Cohen's d for t-tests, with values of 0.1, 0.3, and 0.5 and 0.2, 0.5, and 0.8, being considered small, medium and large effect sizes, respectively (Cohen, 1992). Statistical analysis were performed using SPSS for Macintosh, version 23 (SPSS Inc, Chicago, IL).

Ethical considerations

The study was conducted in agreement with the Helsinki Declaration and was approved by the Regional Committee for Medical Research Ethics in South East Norway (2013/407). Written informed consent was obtained from all healthy controls, the patients' next of kin in paper 1 and III, and from those patients capable of providing informed consent at follow-up in paper III. All patients included had suffered brain injuries in the most severe range. Although the research ethics board approved the study and thus allowed legal exclusion from patient confidentiality, patients without consent from the next of kin were nevertheless not included for ethical reasons. The inclusion process of patients with severe TBI in the sub-acute phase (paper III) included approaching families at a very early time-point after the injury. This required special ethical consideration and a sensitive attitude. The principal investigator, M. Løvstad and myself are both clinical neuropsychologists with long clinical experience with patients with the most severe injuries as well as clinical contact with their families, thus recognizing the extreme and stressful situation the families are faced with at such an early stage. The timing and mode of approaching the families for study inclusion was determined in very close collaboration with an anesthesiologist (author K. Olafsen in paper III) at the neurointensive care unit at OUH, and any special considerations concerning the family's situation was discussed in advance and adjustments taken.

All the included patients with severe TBI in paper III regained consciousness within followup at six months post-injury. For those who gained sufficient cognitive capacity to provide informed consent, a written consent was obtained. One of the key ethical challenges in obtaining informed consent from patients with cognitive deficits after brain injury is the possibility for diminished capacity for informed consent. It is therefore pertinent to ensure that they understand the content of the study, potential risks and benefits, as well as their right to withdraw from study participation. It has been argued that proxy consent should be obtained for research involving cognitively impaired adults when the risks of the research is minimal and the importance of the knowledge to be gained by the research is acceptable (Karlawish, 2003). In our prognostic study of ERP, the patients were not able to give their consent in the early phase after the severe TBI, i.e. the time point for EEG acquisition, but we anticipated that many of them would recover to the degree that they could provide their informed content at follow-up. Hence, the capacity of informed content was evaluated at the timing of follow-up. There are currently no universally accepted guidelines that can be used to assess capacity to consent in patients with acquired brain injury. However, it is recommended to evaluate capacity for informed content by using probing questions to ensure comprehension of the study participation (Johnson-Greene, 2010). Three patients were excluded from the prognostic study of ERP (paper III) due to lack of cooperation during the phase of post-traumatic confusion, as it was considered ethically problematic to proceed with further EEG-recordings.

It was important that both the close family member giving their proxy consent, as well as the patient, felt treated with the necessary professional care. With all patients in prolonged DoC, the responsible healthcare institution and the families were offered information about the clinical assessment along with clinical advice. We often arranged for a collaborative meeting the same day as conducting the ERP recording and the clinical assessment of level of consciousness. When needed, a written report of the clinical evaluation was offered. All TBI patients included in the prognostic study (paper III) were offered information of neuropsychological test results, and when needed, a neuropsychological report was written. In some cases, referral for further clinical follow-up was recommended to the patient's GP. None of the participants withdrew their consent during the study.

Summary of papers

Paper I

Background: ERPs have shown promise in detecting residual covert cognitive capacity without behavioral requirements in patients with disorders of consciousness (DoC). However, the diagnostic utility of ERP remains to be established at an individual patient level, and there is need to determine what constitutes the most robust experimental paradigm to elicit electrophysiological indices of covert cognitive capacity.

43

Methods: Two tasks encompassing active and passive conditions were explored in an event related potentials (ERP) study. The active tasks included (1) active listening for a change of pitch in the subject's own name (SON) and (2) active counting of SON, randomly interspersed unfamiliar name (UN). Both tasks were contrasted to a passive listening condition, and all four conditions were presented in the same hierarchical order. Task robustness was studied in 20 healthy controls, and the utility of the active tasks to detect signs of command-following at an individual patient level was investigated in 20 patients in a minimally conscious state, either showing (9 MCS+) or lacking (11 MCS-) behavioral response to command.

Hypothesis: In the healthy control group, it was expected that the salient value of SON would elicit more pronounced responses compared to UN. It was furthermore anticipated that SON would elicit a larger P3 in active compared to passive tasks. The second aim was to compare patients in MCS+ and MCS- with regard to P3-amplitudes in the active versus passive conditions, wherein it was expected that more patients in the MCS+ group compared to MCS-would demonstrate an enhanced P3 in the active conditions. It was furthermore expected that electrophysiological indices of command-following would be observed in a minority of patients in MCS-.

Main findings: As expected, a larger P3 response to SON compared to UN was found in the healthy control group. Furthermore, the healthy control group also demonstrated a larger P3 response in the counting task compared to active listening to pitch. At an individual level, the counting task also detected a higher rate of electrophysiological response to command compared to the pitch-task (counting task: 19/20 responders, pitch-task: 15/20). In the patients with MCS, the counting task also detected higher rates of electrophysiological indicators of command-following at an individual patient level compared to the pitch-task (counting task: 9/20, pitch-task: 4/20). Moreover, 4/9 MCS+ and 5/11 MCS- demonstrated electrophysiological response to command in the counting task. Thus, 45% of the patients demonstrated signs of command-following in electrophysiological recordings, despite not doing so behaviorally.

Conclusion. This study confirms that the use of an ERP-paradigm involving actively counting SON contrasted to a passive listening task is robust in probing for volitional cognitive capacity in both healthy controls and patients in MCS, yielding supplementary information about covert cognitive resources in some patients.

Paper II

Background: Advances in neuroscientific methods has led to optimism regarding potential clinical utility in diagnostic considerations in patients with DoC after severe acquired brain injury. This is in part due to several studies indicating that residual cognition can be detected with imaging techniques despite absence of behavioral signs of consciousness. However, it is still not established how close are we to implement these methods in the clinical setting. Methods: The systematic literature review examined the diagnostic utility of electrophysiological recordings during active cognitive tasks in detecting residual cognitive capacities in patients with DoC. A systematic review of empirical research published between January 2012 and March 2016 was performed in the Medline, Embase, PsycINFO, and Cochrane databases. Data extracted included sample size, electrophysiological technique, task design, calculations of sensitive and specificity rates, rate of persons with definite voluntary behavioral responses, but no clear signs of cognitive effort in electrophysiological assessments (false negatives), rate of patients demonstrating signs of command-following in electrophysiological recordings, despite not doing so behaviorally (false positives), and number of subjects excluded from analysis. Sensitivity was understood as the ability to detect electrophysiological signs of consciousness in patients with discernible behavioral signs of consciousness. Specificity was understood as the ability of electrophysiological techniques to accurately identify patients who show no or only low-level signs of consciousness (e.g. visual pursuit), but not behavioral command-following (VS and MCS-), and whom fail to demonstrate neurophysiological signs of command-following. The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) was used for quality appraisal. Hypothesis: It was anticipated to find heterogeneity in study design and variability in the robustness of active tasks used in the included studies, and therefore likely that metacalculation of sensitivities and specificities across varying methods and experimental conditions would be ineffectual. It was expected to find reports of false negatives and false positives in the included studies, with relevance for the overall evaluation of the clinical diagnostic utility of electrophysiological techniques in patients with DoC. Main findings: Twenty-four studies were included. Sensitivity rates in healthy controls demonstrated variable accuracy across studies, ranging from 71% to 100%. In patients with DoC, specificity and sensitivity rates varied from 0% to 100%, demonstrating that not all patients with behavioral command-following were classified as responders based on their electrophysiological activity (false negatives). Specificity rates varied markedly, also ranging

from 0% to 100%. This could be related to small sample sizes, or implying that some patients show signs of command-following in electrophysiological recordings, despite absence of behavioral command-following (false positives). Pronounced heterogeneity was found between studies regarding methodological approaches, task design and procedures of analysis, rendering comparison between studies challenging.

Conclusion: We are still far from establishing precise clinical recommendations for standardized electrophysiological diagnostic procedures in assessment of patients with DoC, and high levels of artifacts remain an issue of concern. In summary, one needs to cautiously balance the risk of false positive versus false negative diagnostic errors in individual assessments, as it is evident that a patient with discernible signs of behavioral command-following can appear as a false negative electrophysiologically. However, in cases where factors such as severe motor deficit causes diagnostic uncertainty, electrophysiological methods may add valuable supplemental diagnostic information of covert cognition in some patients with DoC.

Paper III

Background: Predicting outcome in the early phase after severe TBI is a major clinical challenge, particularly with regard to identifying patients with potential of good cognitive outcome. ERPs have shown some promise in aiding prognostication, but there is scarce knowledge of the prognostic utility of ERPs beyond mere awakening from coma and detection of consciousness. The main aim of the present study was to investigate residual cognitive capacity using ERPs in the sub-acute phase after very severe TBI, and to explore the association between ERPs and outcome at six months post-injury.

Methods: Fourteen adult patients with very severe TBI were recruited from the neurointensive care unit (mean age=38.2 years; 8 males; mean lowest GCS score within first 24 hours=5.4). Sub-acute EEG-recordings were conducted biweekly at three time-points applying the same ERP paradigm as in paper I, consisting of a passive condition involving just listening to SON randomly interspersed between an UN, and an active condition with instruction to count SON. Presence and normalization of cognitively mediated P3 responses were explored, along with investigation of the relationship between P3 recorded sub-acutely and six months outcome. Functional and cognitive outcome six months post-injury was measured with GOSE and neuropsychological tests of IQ, attention, memory and executive functioning. *Hypothesis:* It was anticipated that cognitive P3 to SON elicited in an active task could be

detected at an individual level in the sub-acute phase. It was furthermore expected that

presence of P3 to SON in the active task would be related to better functional and cognitive outcome six months post-injury.

Main findings: Ten patients demonstrated a significantly enhanced cognitive P3 in the active counting task compared to passive listening across sub-acute recordings, and six patients presented with normalization of P3 in the active task. Moreover, P3-amplitude elicited in the active task at T3 was positively correlated with both functional outcome (GOSE) and cognition (verbal learning, attentional set-shifting and switching) six months post-injury. *Conclusions:* ERP can index cognitive capacities in the sub-acute phase after severe TBI. The cognitive P3 component in an active design is furthermore associated with functional and cognitive outcome, demonstrating that P3 may yield valuable information of residual sub-acute cognition, and provide supplementary prognostic information.

Discussion

The main aim of the thesis was two-fold:

- Firstly, the clinical diagnostic utility of electrophysiological methods in patients with DoC following acquired brain injury was investigated.
- Secondly, the prognostic utility of cognitive ERPs recorded sub-acutely following severe TBI was examined.

The first objective was examined in paper I by applying two active ERP-tasks with different cognitive load, both compared to passive listening. More specifically, the P3-difference between active and passive tasks was investigated at an individual level both in healthy controls and a group of patients in stable MCS. In paper II, the clinical diagnostic utility of electrophysiological techniques applying active tasks in patients with DoC was investigated in a systematic literature review. Prognostic utility of cognitive ERPs recorded sub-acutely following severe TBI was examined in paper III, which included repeatedly recorded ERPs in combination with an active counting task in the sub-acute phase following very severe TBI, using the same experimental ERP design as in paper I. Presence of a P3 response in the active task, ERP normalization, and the correlation between the cognitive P3 component and functional and cognitive outcome was investigated in a group of patients in the most severe range of TBI. Thus, this thesis forms part of a research tradition that aims at exploring the clinical utility of techniques that provide online monitoring of cognitive function without requiring motor behavior.

Diagnostic utility of electrophysiological methods in patients with DoC

ERP and the robustness of two distinct active tasks

Paper I investigated the robustness of two distinct active ERP-tasks (see figure 4) in both healthy controls and patients in a stable MCS. The first active ERP-task involved the instruction to listen to a change in pitch to subject's own first name (SON). The second active ERP-task involved the instruction to count SON randomly interspersed between an unfamiliar name (UN). Both active tasks were contrasted to passive tasks. In the inquiry of which of the two ERP-tasks constitutes the most robust paradigm among healthy controls, the study found both a markedly larger N1 and P3 potential for the active task involving counting of SON, compared to active listening to pitch. This was confirmed when exploring the rate of individual responders, i.e. subjects displaying electrophysiological signs of commandfollowing across the two tasks among the healthy subjects, showing a 95% responder rate in the counting task, as opposed to a 75% responder rate in the task with the instruction to listen for a change in pitch. The responder rate of healthy controls in the pitch-task is in line with the previous study of Schnakers et al., (2015), where a 79% responder rate was demonstrated in healthy controls while using the same pitch-task. The necessity of including personally relevant stimuli has previously been strongly emphasized, as the probability of eliciting electrophysiological responses in patients with DoC increases with salient self-referential stimuli (Laureys et al., 2007), and the SON has proven promising in this regard (Cavinato et al., 2011; Fischer, Dailler, & Morlet, 2008; Fischer et al., 2010b; Perrin, Garcia-Larrea, Mauguiere, & Bastuji, 1999; Perrin et al., 2006). The current study revealed a larger P3 to SON compared to UN in the control group, confirming the robustness of including salient stimuli. However, higher sensitivity rate in the healthy controls for the counting task compared to listening for pitch demonstrates that the cognitive content of the active condition is of importance, as the instruction to count SON proved to be more robust, thus replicating previous high sensitivity rates for the counting task in healthy subjects (Schnakers et al., 2008). The robustness of the counting task was also reflected in the patient group, with more than twice as many responders in the counting task (9/20) compared to actively listening for change in pitch (4/20). Furthermore, in paper II, a systematic review of rates of individual responders in healthy controls across the 24 included studies applying active tasks during electrophysiological recordings was undertaken. It was found that far from all

electrophysiological studies have shown 100% accuracy in healthy controls, but the instructions of counting an auditory target stimuli, either SON (Hauger et al., 2015; Schnakers et al., 2008) or a global deviant (Bekinschtein et al., 2009; Faugeras et al., 2011; King et al., 2013), showed replicated evidence for strongest robustness.

When considering the robustness of active tasks, the well-replicated local-global paradigm is of particular interest in populations with DoC. The local-global paradigm consists of a series of tone sequences containing a 2-level structure of occasional irregularities in short-term ("local") violations within a 5-sound sequence, and long-term ("global") violations of the expectancies of such sequences (Bekinschtein et al., 2009). In this paradigm, the detection of auditory global deviants is thought to only be present when subjects consciously perceive this global rule violation. This global effect has been proven to be robust in healthy controls, but importantly, the paradigm has also shown capable of detecting such global effect in a minority of patients with no behavioral signs of consciousness (Bekinschtein et al., 2009; Faugeras et al., 2011; Faugeras et al., 2012; King et al., 2013; Sitt et al., 2014). Thus, the local-global paradigm represents an elegant electrophysiological design encompassing simple auditory sounds, without the use of self-referential stimuli. Hence, the local-global paradigm contradicts the notion that it is necessary to include salient stimuli, such as SON, in order to elicit electrophysiological signatures of active cognitive processes in patients with DoC.

However, a recent study has shown responses to global deviant in comatose patients following cardiac arrest, subjects that by definition of their comatose state are not conscious (Tzovara, Simonin, Oddo, Rossetti, & De Lucia, 2015). The authors concluded that the global effect was present in 10 out of 24 comatose patients, which challenges previous assumptions that the global effect can only be observed in conscious and attentive subjects. However, the global effect was only found in six out of 21 healthy controls in this study, i.e. a high rate of false negatives, contrary to previous findings. This indicates a possible methodological flaw in this replication study. The conflicting results across studies have led to a debate about divergence in design and methodological approaches in the mentioned studies applying the local-global paradigm (Naccache et al., 2015; Tzovara, Simonin, Oddo, Rossetti, & De Lucia, 2015a; Tzovara et al., 2015b).

Diagnostic accuracy of electrophysiological methods in patients with DoC

Clinical misdiagnosis of patients with DoC is an ever-present concern. Although neurophysiological techniques have shown promise with regard to diagnostic value, it has not been well described to what extent the combination of experimental paradigms with active tasks during electrophysiological recordings can complement standardized behavioral assessment. In the systematic review in paper II, rates of sensitivity and specificity in patients with DoC were investigated across the included studies that applied active cognitive tasks during electrophysiological recordings. Sensitivity rates in patients with DoC varied markedly, ranging from 0% to 100%, with a subsequent effect on the rates of false negatives, discussed below. Of note, the 100% sensitivity rate was in several studies the result of samples consisting of one single MCS+ responder. Specificity rates also varied markedly, ranging from 0% to 100%, also here possibly related to small sample sizes or to the fact that behavioral measures, in some cases, fail to detect the true level of cognitive functioning in the patient.

False negatives and -positives in detecting electrophysiological signs of command-following False positives and false negatives, also recognized as type I and type II errors, represent a divergence in the test results from the actual phenomenon. A false positive occurs when evidence of an effect is measured, yet the target phenomenon is absent from the test condition (false alarm). Conversely, a false negative (miss) occurs when an effect is not measured even though the target phenomenon is, in fact, present in the test condition (Tabachnick, 2014). Thus, the rate of false positives and false negatives is linked to the estimation of sensitivity and specificity of a diagnostic test. If a test detects every occurrence of a target phenomenon, it is 100% sensitive. Yet, false positive results may be present. On the other hand, a test is 100% specific if it accurately differentiates between true and false positives. However, true estimates of sensitivity and specificity of electrophysiological techniques designed to detect residual awareness in brain-injured patients is problematic due to the lack of independent methods for checking the correspondence of test results with the true level of consciousness in these patients, i.e. there is no established gold standard measure of consciousness (Giacino et al., 2014; Peterson et al., 2015). The electrophysiological test results were compared to the level of consciousness established with the best available standardized behavioral assessment tool, i.e. the CRS-R, as the reference standard.

The systematic review demonstrated a wide variability in rates of false negatives, from 0 to 100%, indicating on average that maybe as many as one third of the patients who presented with unequivocal behavioral responses to command (patients being categorized as MCS+ according to the CRS-R scoring), were not classified as responders based on their electrophysiological activity. Interestingly, the two largest studies included in the systematic review demonstrated false positive rates of 17% (King et al., 2013) and 33% (Sitt et al., 2014), inferring in this context, that some patients show signs of command-following in electrophysiological recordings, despite not doing so behaviorally. In paper I, the counting SON-task demonstrated false positive rates of 45%, where five of 11 patients in MCS- with absence of behavioral command-following were considered responders in the active ERPtask. This represents a larger rate of false positives compared to the two largest studies included in the systematic review in paper II (King et al., 2013; Sitt et al., 2014). This could be explained by the fact that paper I only included patients in MCS, while the two large studies of Sitt et al. (2014) and King et al., (2013) also included patients behaviorally diagnosed as being in VS. Inherent to the diagnostic distinctions between MCS and VS, it is likely that more patients in MCS compared to VS possess residual cognitive resources that cannot be detected behaviorally, i.e. command-following. In summary, the findings in paper I and II suggest that electrophysiological techniques, such as ERP, can detect covert cognitive resources in some patients with DoC when the experiments are properly designed. Correspondingly, the term "cognitive motor dissociation" (CMD) has recently been used in describing patients having a bedside examination consistent with coma, vegetative state or the limited volitional behaviors seen in minimally conscious state, who are unable to follow commands behaviorally, but demonstrate command-following with use of functional brain imaging- or electrophysiological techniques. Thus, these are patients showing motorindependent signs of covert cognitive resources (Schiff & Fins, 2016). ERP may thus supplement standard behavioral assessment for more accurate diagnosis. Accurate diagnosis is crucial for tailoring the daily management of the individual patient, rehabilitation planning, pain management, and handling of end-of-life decisions, but also for prognostication, as outcome in MCS patients is significantly more favorable on average, relative to VS (Giacino et al., 2009). However, we are far from providing exact recommendations for clinical procedures for ERP. In the absence of a gold standard for measuring consciousness, when using active neurophysiological techniques, such as ERP, one must be aware of the possibility and risk of both false-positive and false-negative errors. Electrophysiological techniques are

not at a point where they can reliably replace standardized behavioral methods, but can only supplement them, and provide additional information in some, but not all, patients.

Prognostic utility of cognitive ERPs in severe TBI

Use of ERP in detecting sub-acute signs of residual cognitive capacity

Paper III investigated the value of using ERP for detecting residual cognitive capacity in the early phase after very severe TBI, and explored the association between ERPs and outcome six months post-injury. Herein, the presence and normalization of cognitively mediated P3 responses in the active counting task during three sub-acute EEG-recordings was explored. Ten patients demonstrated a significant P3-difference in the counting task compared to passive listening across the recordings, demonstrating that this neurophysiological method encompassing active experimental conditions, can tap into residual cognitive functioning in patients with severe TBI in the sub-acute phase, long before standardized neuropsychological assessment is feasible. The P3-amplitude difference even preceded overt evidence of command-following in two non-communicating patients in MCS-. This latter finding is in line with studies demonstrating electrophysiological signs of covert cognitive resources in patients with DoC (Bekinschtein et al., 2009; Faugeras et al., 2011; Schnakers et al., 2015; Sitt et al., 2014). Thus, electrophysiological probing for residual cognitive capacity may in some cases go beyond what can be elicited in clinical evaluations using behavioral methods, be it CRS-R or neuropsychological tests.

Furthermore, six patients presented normalization of P3 in the counting task. In the normalization-group there was a significantly larger P3-amplitude to SON in the active task at T3 compared to T1, and the P3-amplitude was significantly larger in the active task compared to the passive at T3, which was not found in the non-normalization group. In a large cohort of patients enrolled in a TBI Model System study (Nakase-Richardson et al., 2012), 56 to 85% (depending on functional independence item) of patients with severe TBI who were admitted to acute inpatient rehabilitation with no command-following, but with subsequent early return to consciousness, achieved independence on one or more functional domains by 5 years post-injury, versus 19 to 36% of those who did not have an early regained consciousness (Whyte, Nakase-Richardson, et al., 2013). Normalization of the P3 response to SON in an active task may indicate early signs of cognitive recovery, and thereby provide supplemental prognostic

information, as recovery of cognitive functioning is one of the key goals for outcome after severe TBI.

Association between sub-acute P3 response in active task and outcome

In paper III it was demonstrated that P3-amplitude to SON in the counting task at T3 was positively correlated with both functional outcome (GOSE) and cognition (verbal learning, attentional set-shifting and switching) six months post-injury. Predicting outcome at an individual patient level in the early phase after severe TBI is a major clinical challenge, particularly when attempting to identify patients with potential for good cognitive outcome. Even though the validated prognostic models IMPACT and CRUSH have the advantage of offering prognostic calculations at an individual patient level (Castano-Leon et al., 2016; Steverberg et al., 2008), they are criticized for mainly predicting unfavorable outcome, and also overestimating mortality (Olivecrona & Olivecrona, 2013; Sandsmark, 2016). However, early and reliable recognition of those who might regain good cognitive outcome is essential for treatment planning. While early evoked potentials and presence of ERPs (using passive experimental conditions) can provide prognostic information of negative outcome in the acute phase (Lew et al., 2006; Robinson et al., 2003; Wang et al., 2004), and informing on probability of awakening from coma (Daltrozzo et al., 2007), the results in this study indicate that the P3 component elicited in a cognitive active task in the sub-acute phase may index functional and cognitive recovery. However, the exact sensitivity and specificity of the technique for providing accurate prognostication at an individual patient level remains unknown and further studies are warranted. With regard to the prognostic utility of active ERP designs in severe TBI, further methodological developments are needed in order to implement these methods into clinical practice.

Outcome diversity in patients with severe TBI

The measured outcomes of the included patients in paper III indicated substantial heterogeneity in functional level six months post-injury. This is in line with previous studies of outcome following severe TBI (Anke et al., 2015; Jourdan et al., 2016; Ponsford et al., 2008). Hence, there is a need for more precise prognostication at a single-patient level in the early phase even in the most severe category of TBI, as the initial severity of the TBI, as routinely measured by the GCS, does not sufficiently predict patient outcome. Also, prognosis of mortality and unfavorable outcome are insufficient, as some patients with severe TBI have good functional and cognitive outcomes. Of note, in a national Norwegian cohort of 163

patients with severe TBI, 90% lived at home and 10% at nursing homes one year post-injury (Anke et al., 2015). A major goal is to identify patients with the prospect of good outcome following severe TBI, and to better tailor treatment plans in order to optimize the rehabilitation course for the individual patient. Importantly, studies have shown that better functional outcome occurs in patients with severe TBI who receive early onset and a continuous chain of rehabilitation (Andelic et al., 2012; Choi et al., 2008). Furthermore, it is important to be aware of the reported self-perceived unmet needs regarding long-term cognitive and emotional difficulties among patients with moderate to severe TBI, despite patients reaching favorable functional outcomes (Andelic, Søberg, Berntsen, Sigurdardottir, & Røe, 2014).

Methodological issues

Interpretation of negative electrophysiological findings

At the time of planning of the study, a decision was made to apply the same ERP design, encompassing two different active conditions, for both studies of paper I and III. With the gained knowledge regarding task robustness, only the counting condition contrasted to passive listening was used for statistical analysis for paper III. However, the extensive ERPparadigm was applied in the included patients. One may hypothesize that exposing the patients to the extensive ERP-paradigm may have caused unnecessary fatigue, and thus may have influenced their electrophysiological response in the counting task, potentially influencing the lack of significant difference in P3-amplitude between the active counting task and passive listening in as many as 23 of the total of 42 recordings across the three subacute time-points. In addition, the majority of negative findings was in patients presenting with PTCS or regained orientation, that is, patients whom had emerged from DoC and were behaviorally capable of simple command-following. On the other hand, there are several other issues that may influence the lack of significant P3-difference. Performing repeated ERPs in the sub-acute clinical setting is complicated. For instance, in the ICU, the EEG-recordings might be interrupted by critical medical events, or the patient might be characterized by motor restlessness, all hazards to EEG quality. Also, lack of cognitive ERP responses in patients with the most severe acquired brain injuries may be due to underlying symptoms such as cognitive impairments, deficits in language, attention, memory, executive functioning, cognitive drive, as well as behavioral impairments characterized by reduced motivation and lack of cooperation, all potentially preventing them from performing successfully in active

tasks requiring effortful cognitive processing during electrophysiological recordings, with the risk of producing false negatives. Consequently, due to the potential presence of confounders, it has been argued that negative EEG findings in patients with DoC cannot be interpreted as evidence that the patient lacks awareness (Bardin et al., 2011; Gibson et al., 2014).

Active ERP-tasks with requirements for language perception

Although ERP studies using active tasks probing for consciousness in patients with DoC are promising, a methodological concern is the requirements for patients to adequately perceive and process linguistic instructions. A previous functional connectivity study using PET has shown possible underlying language deficits in patients in MCS- compared to MCS+, showing that patients in MCS- had metabolic dysfunction in the dominant left-hemispheric language network compared to patients in MCS+ (Bruno et al., 2012). Hence, there is a need for robust test procedures that are not restricted by either motor responses or language comprehension. Of note, new alternative ways of investigating consciousness are currently being developed, potentially bypassing the need to attend to external stimuli. The most promising technique combines transcranial magnetic stimulation (TMS) and high-density EEG, which allows assessment of the complexity and the functional connectivity of brain responses to TMS pulses (Massimini, Ferrarelli, Sarasso, & Tononi, 2012). In patients with DoC, it has been demonstrated that the response elicited to TMS pulses in patients in VS are restricted to slow wave stereotypical EEG responses below the stimulated area. By contrast, MCS patients showed more complex EEG responses, which were more widespread to largedistance and contralateral areas, indicating more intact cerebral networks (Rosanova et al., 2012). Herein, a perturbational complexity index (PCI) can be used to quantify the difference in TMS-EEG responses present between states of consciousness and states of unconsciousness. Indeed, Casali and colleagues showed that the PCI has the potential to discriminate the level of consciousness at a single subject level in patients with DoC, without the requirements of active mental processing and language comprehension (Casali et al., 2013). However, these are highly complex methods that are not readily available in the clinical setting, and the findings are in need for replication in large-scale multi-centric studies.

Variation in electrophysiological techniques and tasks across studies

It has previously not been well described which type of experimental procedure or electrophysiological measure that are the most robust and best suited in investigating residual cognitive capacity in patients with DoC. In the systematic review in paper II, heterogeneity with regard to study designs as well as variability in the robustness of active tasks used in the included studies was anticipated. The included studies did display a wide variation in the applied electrophysiological techniques, with the majority being EEG-based technology. Furthermore, the systematic review revealed considerable heterogeneity in the types of active experimental paradigms applied, where the majority were either imagery tasks or tasks requiring counting an auditory target stimulus. Due to the wide heterogeneity, the conditions necessary to conduct meta-calculation of sensitivities and specificities across varying methods and experimental conditions were not fulfilled, thus, limiting the synthesis of extracted data. Importantly, ERP studies using active tasks probing for consciousness in patients with DoC includes verbal instructions and the requirements for language perception. The abovementioned method combining TMS and high-density EEG requires no specific language perceptions and measures level of brain connectivity while resting instead of electrophysiological signatures of active mental processing. At present, the TMS with highdensity EEG probably constitutes the most promising neuroscientific technique with promise for future supplement to standard behavioral diagnostic assessment at an individual patient level. Combining simultaneous fMRI and ERP is theoretically a potentially potent method, but both are prone to movement artifacts in severely brain-injured patients (Bodien & Giacino, 2016; Peterson et al., 2015), and simultaneous recording will therefore be particularly challenging in the DoC population. We are not aware of any studies of DoC that have applied simultaneous recording of ERP and fMRI.

The issue of blinding in electrophysiological studies probing for residual cognition

A further methodological challenge is the issue of blinding. There is no strong tradition within electrophysiological research of blinding the assessors, likely because electrophysiological recordings are not expected to be biased by rater expectations. However, there is a fair amount of subjective evaluation in processing and interpretation of ERP data, rendering reason for bias concern when investigating diagnostic accuracy of ERP methods.

Automated machine-learning techniques or systems for brain-computer interface (BCI) have the benefit of being less influenced by the bias issue of blinding. In command-following paradigms, a classifier's performance score assesses the patient's ability to follow command. As such, EEG-based machine-learning techniques for classifying disorders of consciousness involves computer-learning of the relation between a set of different input EEG-features and pre-established target labels or classes, e.g., healthy controls with normal awareness, MCS and VS (Noirhomme et al., 2015). As these methods are based on classifier algorithms, they are less influenced by the issue of blinding, that is, whether the researchers conducting the electrophysiological assessment was blinded to the behavioral assessment, and vice versa.

Patients sample sizes

Patients with persistent DoC are a low-frequent patient group (Løvstad et al., 2014), and hence it took 3 years and 1 month to include the eligible patients in the study reported in paper I. The final sample of nine patients in MCS+ and 11 in MCS- was of small to medium size compared to the electrophysiological studies included in the systematic review of paper II. The sample sizes ranged from very small samples of only six included patients to the largest study with a total of 167 electrophysiological recordings acquired from 113 patients. The limited final sample size of fourteen patients with severe TBI in paper III was not intended. However, it proved more difficult than expected to recruit consecutive patients with severe TBI from the neurointensive care unit. Lack of compliance from next of kin to give consent at such as early stage after the trauma was somewhat surprisingly not a major issue, as this was only the case in two patients. Conversely, of the total of 76 patients with GCS lower than 9 evaluated for study inclusion, the majority were excluded due to insufficient fluency in Norwegian language prior to the injury, severe psychiatric or substance abuse disorders in need of treatment, hemicraniectomy, and high age.

The electrophysiology of lesioned brains

ERPs are one of the most informative and dynamic methods of monitoring information processing in the brain, and offer the temporal resolution necessary to capture neural processes associated with the cerebral substrates of cognition (Duncan et al., 2011; Mazzini, 2004). In the context of this thesis, the methodology has the advantage of being applicable to non-communicating patients with severe acquired brain injuries, who often present with major sensorimotor deficits, and thus provides a means to evaluate patients not suitable for conventional neuropsychological assessment. It has been summarized that injury severity is associated with reduced amplitudes of auditory N2b and P300, and increased latencies of auditory P300, at least in severe TBI (Duncan et al., 2011), as later and cognitively mediated ERP potentials, such as P3, is sensitive to pathological mechanism of the injured brain (Reinvang, 1999).

Decreased P3 amplitude combined with potential confounders of EEG-quality in patients with the most severe brain injuries, such as artifacts caused by involuntary movements, challenge the signal to noise-ratio, which might influence the likelihood for detecting a robust and unequivocal P3-response at an individual level. Another issue is the reliability of ERPs in patients with severe brain injuries. Studies investigating test-retest reliability of the P3amplitude in healthy subjects have shown variable results, ranging from 0.31 to 0.93, although the majority of studies have reported moderate-to-strong reliability estimates over periods ranging from weeks to years (Cassidy, Robertson, & O'Connell, 2012; Walhovd & Fjell, 2002). Schorr and colleagues (2015) investigated the retest reliability of ERPs with repeated tests at four different time-points in patients with DoC (of mixed etiology) and a group of healthy controls. An auditory oddball paradigm presenting rare, target high-pitch tones (20%) randomized with standard low-pitch tones was applied, while instructing both controls and patients to pay attention to the high-pitch tones and count along silently in their minds. They found that the number of identifiable P3 responses varied between zero and four in both groups (controls: 56.25 % of total testing sessions, patients with DoC: 35.42%), suggesting a general instability of the of P3 occurrence in patients with severe brain injury, but also in healthy controls. However, the low P3 occurrence in the patient group was lower than the total of the pooled P3 responses found in the patient group in paper III (Schorr et al., 2015). The lower P3 occurrence in the study of Schorr et al. could possibly be explained by the lack of salient stimuli used in their ERP design.

Clinical implications

Accurate assessment of level of consciousness and residual cognitive capacity in patients with the most severe acquired brain injuries is paramount for enabling the establishment of realistic and adequate treatment plans. For patients with severe TBI, there is a need to direct attention to those patients showing early signs of cognitive recovery with potential for good functional and cognitive outcome, as the results in paper III replicated that there is a wide variety in outcome even in the most severe range of TBI. This also needs to be reflected in early treatment decisions and information to families for realistic expectations. In the period immediately following a severe TBI, health care professionals often face critical treatment decisions, and even predicting survival can be incredibly challenging. Modern electrophysiological techniques may provide supplemental information for improved diagnostic and prognostic accuracy in patients with the most severe acquired brain injuries. In summary, patients with DoC present with medical complications that require specialized brain-injury medical expertise, along with diagnostic and prognostic challenges in need of expert assessments. Thus, patients with DoC should be offered treatment in centralized intensive rehabilitation facilities with expert knowledge and multi-disciplinary teams.

In Norway, a continuous chain of rehabilitation for severe brain injuries starting from the acute phase to the sub-acute course is only established for TBI, but unfortunately, it does not include all patients. In a national Norwegian cohort study including 163 patients with severe TBI over a two-year period (2009-2011), only 48% followed a direct pathway to specialized rehabilitation from the acute hospital, 38% had either a broken clinical pathway to specialized rehabilitation or were referred to non-specialized rehabilitation units. Interestingly, the majority of the 13% who were not referred to any in-patient rehabilitation during the first year post-injury had less severe traumas (Sveen et al., 2016). For other etiologies, for example brain tumor, anoxia, stroke or encephalitis, no such continuous chain exists. This implies that patients with DoC of non-traumatic etiologies can be lost to specialized rehabilitation services. Moreover, seriously brain-injured patients are a cost-intensive patient group vulnerable to socio-economic pressures. For patients with prolonged DoC admitted to specialized intensive rehabilitation centers, length of stay can be brief and will often be the only course of rehabilitation offered. Furthermore, after being placed in local chronic care facilities, patients with prolonged DoC are at risk of being lost to long-term follow-up, with potential failure to recognize secondary medical complications or functional recovery. For all patients with the most severe brain injuries and prolonged DoC, a marked improvement in health care services is necessary to ensure expertise in an integrated and comprehensive chain of rehabilitation.

In addition, advancement in diagnosis and prognosis for patients surviving the most severe injuries also raise new ethical questions about withdrawal of life-sustaining treatment, including nutrition and hydration (Fernandez-Espejo & Owen, 2013; Kitzinger & Kitzinger, 2015). Health care professionals' attitudes towards end-of-life decisions vary, however, depending not only on the diagnosis of the patient, but also on the profession and the cultural background of the clinicians, as well as the team's opinion regarding prognosis (Demertzi et al., 2011; Turgeon et al., 2011). In Norway, a national ethical guideline for withdrawal of life-sustaining treatment does not make a clear distinction between VS and non-communicative MCS (Helsedirektoratet, 2013). However, efforts should be made in promoting both ethical

and legal advanced directives for withdrawal of life-sustaining treatment for DoC, as there is no ethical or legal consensus formulated about withdrawing life support for patients in MCS. Hence, it remains an ethical debate as to how treatment limitations should be applied for patients in MCS.

Conclusion and future directions

This study demonstrates that cognitive ERPs elicited in an active task may provide supplemental diagnostic information in patients with DoC, can be informative regarding subacute residual cognitive capacities in patients with severe TBI, and provide prognostic information of their relation to functional and cognitive outcome. With regard to diagnostic contribution for patients with DoC, we are still far from establishing precise recommendations for standardized electrophysiological diagnostic measures. A necessary step in future research is to initiate multicenter studies, providing comparable data sets with large sample sizes across laboratories, and to further establish valid sensitivity and specificity estimates. Herein, ensuring systematic validation of electrophysiological paradigms in healthy controls is essential. Thus, standardized behavioral measures still constitute the standard approach for diagnostic assessment in patients with DoC.

With regard to cognitive ERP's utility for prognostic information, unsolved methodological issues, such as EEG-artifacts, and potential confounders, such as underlying cognitive deficits and lack of cooperation, suggest that further research is needed before cognitive ERP methods should become routine in prognostic evaluations. A current barrier to clinical implementation of ERP-designs encompassing active tasks is also lack of sufficient knowledge of sensitivity and specificity rates. In the future, the combination of behavioral, electrophysiological and imaging methods will all possibly contribute in improving diagnostic and prognostic accuracy.

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