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Publication date:
2007

Document Version
Publisher's PDF, also known as Version of record

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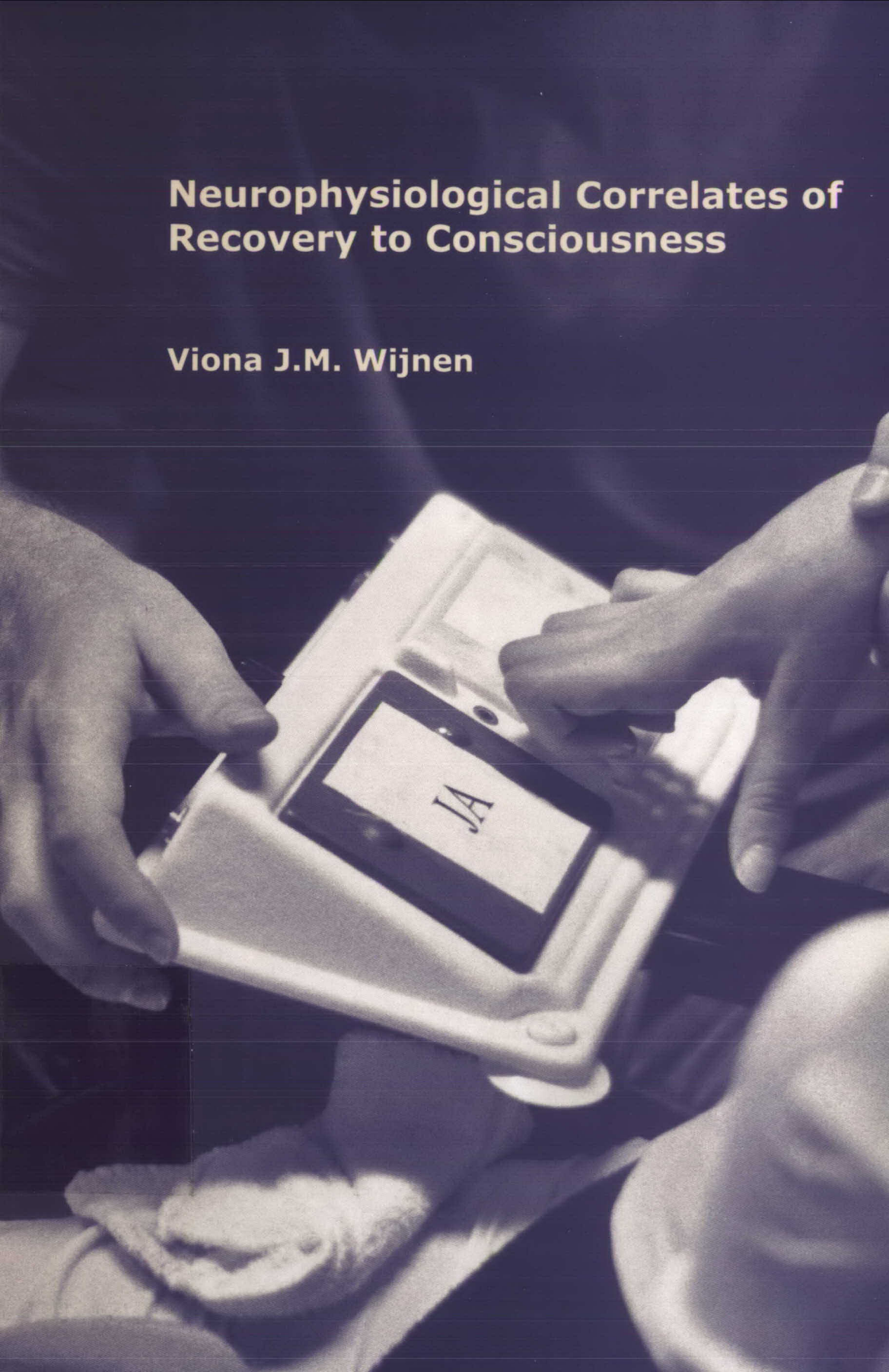

Neurophysiological correlates of recovery to consciousness

The research presented in this thesis was performed at the Rehabilitation Centre Leijpark in Tilburg, The Netherlands, in cooperation with the Tilburg University, The Netherlands. The study was financed by Stichting Centraal Fonds RVVZ, Johanna Kinderfonds, CZ groep Zorgverzekeringen, Zorgverzekeraar VGZ, Zorg en zekerheid, Stichting Bio Kinderrevalidatie, and Hersenstichting Nederland.

Druk:  Ridderprint, Ridderkerk

ISBN/EAN: 978-90-5335-132-1

Cover:
The cover photo was made by Willie-Jan Staps. It is one of the photos of a photo-shoot performed for the book 'Een knuffel van Christel' (A cuddle toy of Christel), by Henk Eilander & Jacobien Erbrink. The book (in Dutch) concerns the development and contents of the Early Intensive Neurorehabilitation Programme. It also describes the story of the first patient (Christel) who particpated in this programme. In fact, the programme was developed in order to treat patients like Christel.
The photo shows a patient and a physical therapist, helping her to communicate by pushing a yes/no button.

Neurophysiological correlates of recovery to consciousness

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit van Tilburg,
op gezag van de rector magnificus
prof. dr. F. A. van der Duyn Schouten,
in het openbaar te verdedigen ten overstaan van een door het
college voor promoties aangewezen commissie
in de aula van de Universiteit op
woensdag 17 oktober 2007 om 14:15 uur

door

Viona Johanna Maria Wijnen
geboren 11 januari 1973
te Etten-Leur

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Contents

Chapter 1

General Introduction

Introduction

In Quentin Tarantino's motion picture Kill Bill, the main character Beatrix Kiddo (Uma Thurman) suffered a gun shot to her head at her own wedding. She survives the attack on her life, but the bullet causes severe brain injury leading to a coma that lasts four years. When she suddenly awakes from her coma as a result of a mosquito bite, she regains full conscious in an instant, and is determined to take revenge. She is not able to move her legs, but after some physical practice ('wiggle your big toe'), she is soon ready to travel around the world, fighting and killing her attackers one by one. The film beautifully illustrates a number of stereotypes about coma that apparently exists in people's minds, at least in those of popular filmmakers. Coma is often seen as a state of peaceful sleeping, even including closed eyes, which may last for several years. Awakening from coma is likewise often viewed as awakening from sleep; as soon as the eyes are opened, the person is fully aware of his or her surroundings.

Filmmakers may be good in creating stereotypes, but reality is quite different, as anyone who has ever worked with comatose patients will readily confirm. First of all, although severe brain injury such as suffered by Beatrix Kiddo may result in coma, it is highly improbable that the coma lasts that long. If patients do not wake up within a period of about four to six weeks after the injury, the patients either die or enter a *vegetative state* (VS; Jennett and Plum, 1972). In this state the patients seem to be awake but not aware. A sleep-wake cycle exists, but the patients are uncommunicative and unresponsive to the environment. If recovery continues, patients may proceed to a *minimally conscious state* (MCS; Giacino et al., 2002). The patients then begin to show clear but inconsistent evidence of awareness[1] of themselves or their environment, on a reproducible or sustained basis. MCS patients may then recover further, and regain consciousness (Giacino and Kalmar, 2005). In sum, recovery from coma is a slow process and the final outcome is difficult, if not impossible, to predict on an individual level. Unlike the stereotype portrayed in the film, recovery is certainly not sudden with immediate awareness after opening the eyes.

The goal of this thesis is to explore this step-by-step recovery process from the vegetative state to consciousness. It presents a longitudinal study in children and young adults in VS or MCS after suffering severe acquired brain injury. Surprisingly, research on recovery patterns is relatively scarce, especially when young adults are concerned, who are known to be at great risk of severe brain injury (Finfer and Cohen, 2001; Jennett, 1996). The process of recovery from coma to consciousness is therefore poorly understood. The main steps of recovery through VS and MCS described in the previous paragraph are mostly based on clinical observation of behavioural criteria (e.g., movement and language). This does not reveal much about the internal mechanisms of recovery. Exactly *how* the patients regain consciousness is largely unknown, and it comes as no surprise that misdiagnoses of the recovery stages are not uncommon (Andrews et al., 1996; Childs et al., 1993; Zeman, 1997). The present thesis

[1] In this thesis the terms 'consciousness' and 'awareness' are used interchangeably; their content is experience (Zeman, 2000).

focuses on the neurophysiological correlates of the recovery process. Neurophysiological measures, such as brain potentials, heart rate, and electrodermal activity, are simple to record, non-invasive and relatively not too discomforting for the patients. Yet such measurements may reveal much about the mechanisms of the recovery process, even in the absence of overt responding and communication, and as such may also complement the clinical diagnoses based on the observation of behaviour.

Thus, the primary goal was to investigate the relationship between behavioural indices of consciousness and neurophysiological reactivity, during recovery from the VS to consciousness. Two research questions were addressed.

Objective 1: Tracking neurophysiological changes during the stages of recovery.

First, the recovery pattern in general was examined. How do the clinical and behavioural signs of recovery to consciousness correlate with neurophysiological reactivity at different time points during the recovery process? Do the observationally defined stages of recovery correspond to distinguishable neurophysiologically defined stages? Is it possible to refine the diagnosis of the different stages in the recovery process based on neurophysiological measurements? Is recovery a gradual process involving only quantitative changes, or do qualitative changes, as the cleat-cut distinction between the VS and the MCS suggest?

To address these different questions a longitudinal study was undertaken, in which multiple repeated measurements were taken from the same individual patients during various stages of the recovery process. In this way, the whole recovery process could be tracked, from coma to consciousness.

Objective 2: Prognosis for recovery at early stages.

Secondly, differences in the degree in which patients regained consciousness (final outcome) were investigated. Is it possible to separate groups that do and that do not regain full consciousness based on neurophysiological measurements in an early stage of recovery? Final outcome has not been possible to predict based on clinical observation alone, but it would be possible based on neurophysiological measurements, this could have consequences for determining which patients to treat and which patients to withhold an intensive and expensive treatment. Clearly, this is an issue that involves huge ethical and societal dilemmas, but that should not prevent the scientific question being posed whether this is at all possible.

From coma to consciousness: clinical definitions

The patients involved in the studies of this thesis were all victims of a severe acquired brain injury. An acquired brain injury is an injury to the brain that is not hereditary, congenital, or degenerative, and has occurred after birth. Acquired brain injuries can either be traumatic and non- traumatic. A traumatic brain injury is an insult to the brain caused by an external physical force, such as a blow to the head in a traffic accident. Non-traumatic injuries are mostly caused by hypoxic ischemic encephalopathy (Multi-Society Task Force on Persistent Vegetative State, 1994a), e.g. near-drowning, but also cerebro-vascular accidents (CVA; infarct, haemorrhage), drug intoxication, or brain tumours. Table 1 presents the most frequent causes of acquired brain injury.

Table 1 Most common cause of acute traumatic and non-traumatic injuries (Multi-Society Task Force on Persistent Vegetative State, 1994a, p.211)

Traumatic	**Non-traumatic**
	Hypoxic ischemic encephalopathy
	Cardiorespiratory arrest
	Perinatal asphyxia
	Pulmonary disease
Motor vehicle accidents	Prolonged hypotensive episode
Gunshot wound or other form of direct cerebral injury	Near-drowning
	Suffocation or strangulation
Non-accidental injury in children (abuse)	Cerebrovascular injury
	Cerebral hemorrhage
Fall/Blow to the head/Assault (with or without skull fracture)	Cerebral infarction
	Subarachnoid hemorrhage
Birth injury	CNS infection
	Bacterial meningitis
	Viral meningoencephalitis
	Brain abscess
	CNS tumor
	CNS toxins or poisoning

The severity of the acquired brain injury is usually determined by a test called the Glascow Coma Scale (GCS; Teasdale and Jennett, 1974). According to this scale, a score can be obtained by assessing a patient's reaction to stimuli by eye opening, motor function, and verbal response. In brief, the GCS is a test based on observation of behaviour that allows a quick and course distinction of the seriousness of the injury. The terms mild, moderate, and severe brain injury are used to describe the level of initial injury in relation to the neurological severity caused to the brain. A severe acquired brain injury, which is the focus of the current thesis, is defined by a GCS of eight or lower, combined with a state of unconsciousness for longer than six hours: a coma. Appendix 3 describes the Glasgow Coma Scale in more detail.

Another distinction should be made between the *acute* and *post-acute* phase after the injury. The *acute phase* denotes the period immediately after the brain injury up to the moment at which the patient is physically stable and the acute intervention, often at an intensive care

unit, has ended. In this period, the patient is in coma: a deep, sustained pathologic unconsciousness in which the eyes remain closed, and the patient cannot be aroused (Plum and Posner, 1980). The patient responds minimally or not at all to external stimulation, and initiates no voluntary activities. In a comatose state, there is no evidence of awareness of the self or of the environment; nor are cyclical state changes such as a sleep-wake rhythm observed (Schiff and Plum, 2000). Some of the injured will die from the immediate or delayed effects of the severe brain injury without regaining consciousness. Those who survive may remain in coma for four to six weeks (Multi-Society Task Force on Persistent Vegetative State, 1994a).

After four to six weeks, some of the comatose patients progress to "wakeful unconsciousness": the vegetative state (Jennett and Plum, 1972; Laureys et al., 2004a; Multi-Society Task Force on Persistent Vegetative State, 1994a). In this state, the vegetative or anatomic functions, such as breathing, maintaining a normal blood pressure, digesting and eliminating foods are sufficiently preserved to permit survival with medical and nursing care. Because the patient is now physically stable, the *post-acute phase* is said to be entered. In the VS sleep-wake cycles are present, so patients are able to open their eyes, and they can be aroused. However, there are no signs of awareness of the self and the environment and there is the inability to interact with others. A vegetative patient may present verbal sounds (e.g. grunting, moaning, or screaming), motor agitation (e.g. grinding their teeth, grimacing, moving arms and legs), and emotional expression (e.g. shedding tears). However, this behaviour is not sustained, reproducible, purposeful, or voluntary (American Academy of Neurology, 1995). There is no evidence of language comprehension or expression (Multi-Society Task Force on Persistent Vegetative State, 1994a; Royal College of Physicians, 2003). Table 2 lists the criteria that must be met to establish the diagnoses of the VS.

The VS may be a transitory state between coma and consciousness (Beaumont and Kenealy, 2005), but, it may also be permanent. The terms persistent or permanent are used to indicate the duration of the VS. The Royal College of Physicians guidance (2003) proposed that the VS can be regarded as persistent after four weeks. The Multi-Society Task Force on the permanent VS (1994b), defined the VS to be permanent three months after non-traumatic injury or twelve months after traumatic injury. On the other hand, it has also emphasised that the term persistent should be avoided completely, and to describe a patient as having been vegetative for a certain period of time (Jennett, 2005). The diagnosis of permanent VS implies irreversibility, and once this diagnosis has been made, ethical and legal issues around withdrawal of treatment may arise (Jennett, 2005). Therefore, the diagnosis of permanent should be based on clinical rather than temporal considerations alone (Royal College of Physicians, 2003).

In the post-acute phase recovery of the (cognitive) impairments may still occur, spontaneously or by intervention. When patients start to show some voluntary and sustained reactivity to the environment, the minimally conscious state (Giacino et al., 2002) or low

awareness state (Andrews, 1996) is reached. In the minimally conscious state patients have sleep-wake cycles, they are awake for a major part of the day, and they show minimal but definite behavioural evidence of awareness of the self or of the environment (Giacino et al., 2002). For example, patients may have episodes of crying, smiling, or laughter as a response to their family members. Also, cognitively mediated behaviour occurs inconsistently, but is reproducible or sustained long enough to be differentiated from reflexive behaviour (Andrews, 1996). Table 2 shows the criteria for the diagnosis of the minimally conscious state.

Table 2. Diagnostic criteria of the vegetative and minimally conscious states

The vegetative state can be diagnosed using the following criteria, which all must be met to establish the diagnosis (American Academy of Neurology, 1995):
- No evidence of awareness of self or environment and an inability to interact with others - No evidence of sustained, reproducible, purposeful, or voluntary behavioural responses to visual, auditory, tactile, or noxious stimuli - No evidence of language comprehension or expression - Intermittent wakefulness manifested by the presence of sleep-wake cycles - Sufficiently preserved hypothalamic and brainstem autonomic functions to permit survival with medical and nursing care - Bowel and bladder incontinence - Variably preserved cranial nerve (pupillary, oculocephalic, corneal, vestibulo-ocular, gag) and spinal reflexes
The minimally conscious state should be diagnosed when there is clearly discernible evidence of one or more of the following behaviours (Giacino et al., 2002):
1. Simple command-following 2. Gestural or verbal yes/no responses 3. Intelligible verbalisation 4. Movements or affective behaviours 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 behavioural responses: - Episodes of crying, smiling, or laughter in response to linguistic or visual content of emotional but not neural topics or stimuli. - Vocalisation 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. - Pursuit eye movement or sustained fixation that occurs in direct response to moving or salient stimuli.

Object manipulation and functional, accurate communication indicate the emergence from the minimally conscious state (Giacino et al., 2002; 2004a), that is, the recovery of consciousness. Consciousness is reached when patients react adequately to the environment. They have to be able to consistently express goal-directed behaviour (Giacino et al., 2004a). Here, the *chronic phase* starts, in which there is more clarity about what impairments and handicaps will be permanent. However, progression or deterioration can still take place. Many

physical disorders, such as paralysis and motor disorders may be the result of severe acquired brain damage. But also the non-visible disorders in intellect, cognition, emotion, and behaviour may lead to limitations in the daily life of the patient. Only a small percentage of patients who suffered severe acquired brain injury are eventually able to live a completely independent life, in which an education or a job can be resumed (Willer et al., 1991).

Treatment possibilities and the background of the present research

The traditional view on the brain plasticity is that brain cells do not regenerate, and that those that are destroyed are not replaced. However, it has been demonstrated that *our brain is able to change and adapt* constantly as a result of environmental demands. The functions of the parts of the brain that are lost after brain injury can be taken over by other parts of the brain (functional recovery; Luria, 1973). In addition, new brain cells are originate on a daily basis (neurogenesis; Gross, 2000), and new connections can be made between brain cells (sprouting; Merzenich, 2000; Merzenich et al., 1987). The brain has an enormous capacity to respond and adapt to the functional need from the internal and external world (Buonomano and Merzenich, 1998).

The possibilities of recovery from severe brain injury have long been underestimated. The long-held belief was that regeneration, anatomical reorganization and renewal of nervous tissue were impossible in the adult nervous system. About eighty years ago Ramon y Cajal stated that "Once development is complete, the sources of growth and regeneration of axons and dendrites are irrevocably lost. In the adult brain, nervous pathways are fixed and immutably; everything may die, nothing may be regenerated" (Ramon y Cajal, 1928). More recent work suggests that different kinds of growth and regeneration can take place in the damaged brain (Bach-y-Rita, 1980; 2003; Cruikshank and Weinberger, 1996; Gross, 2000; Robertson and Murre, 1999). In a human (adult) brain, new neurons are produced every day, which move through the brain and occupy the place of deceased or redundant neurons. These new neurons apply new connections through the brain and the rest of the body, and involve in various functional processes (Gross, 2000; Levin and Grafman, 2000; Teskey, 2001).

Other recent theories on plasticity involve multiplexing and non-synaptic neurotransmission (Bach-y-Rita, 2003). Multiplexing in the brain consists of multiple uses of neurons and fibres so that these neurons participate in several functions. For instance, in blind Braille readers, tactile processing pathways (usually in the second somatosensory area) are re-rerouted to areas which are originally reserved for visual shape discrimination, such as ventral occipital cortical regions (Sadato et al., 1998). In addition, information in the brain appears to be transmitted both by synaptic connectivity and by non-synaptic neurotransmission, called volume transmission. Information transmission in the brain involving both synaptic and volume

transmission may have considerable relevance to the reorganization of function following brain damage (Bach-y-Rita and Bach-y-Rita, 1990).

The recovery functions of the brain may also be influenced by hormones and pharmaceutics (Bach-y-Rita, 2000), e.g. amphetamines, fluoxetine, methylphenidate, and levodopa (Giacino and Trott, 2004b; Matsuda et al., 2005; Zafonte et al., 2000). In addition, deep brain stimulation may have positive results in some vegetative and minimally conscious patients (Yamamoto and Katayama, 2005), and electrical right median nerve stimulation has recently been found to increase the cerebral blood flow and the level of dopamine, which lead to an improvement of the level of consciousness in coma and VS (Cooper et al., 1999; 2005).

The recovery functions of the brain can also be influenced by environmental information (external stimulation and input). The environment is also an important factor in all mechanisms described above (Bach-y-Rita and Bach-y-Rita, 1990; Robertson and Murre, 1999). Therefore, the recovery processes after brain damage may be enhanced by 'rehabilitation-induced plastic reorganisation' (Robertson and Murre, 1999). Healthy neurons are making new connections constantly, by means of collateral innervations or sprouting, and these processes are being accelerated after damage to the nervous system (Bach-y-Rita and Bach-y-Rita, 1990). In addition, Hebbian cell-assemblies may form after frequently repeating particular stimulations (Cruikshank and Weinberger, 1996; Robertson and Murre, 1999). Hebbian learning describes a mechanism for plasticity wherein an increase in the efficacy of cell connections arises from the frequent communication between cells (Hebb, 1949). When practicing a particular skill, the cells involved will form stronger connections, which cause the skill to become easier to perform.

Experimental studies in animals have shown that 'symptom relevant experience' promotes recovery of visual and motor function in brain injured animals (Gross, 2000). Also, the exposure to an enriched environment following brain injury significantly improves maze-learning performance, relative to performance in animals maintained in 'standard' or 'impoverished' (without any stimulation) environments (Rosenzweig and Bennett, 1996). Animals in the impoverished environments did not recover and some of them even died.

All these lines of evidence suggest that environmental stimulation may be beneficial for recovery from coma to consciousness. As a result, sensory stimulation is often applied as part of the treatment in order to increase the level of arousal and consciousness in vegetative and minimally conscious patients (Tolle and Reimer, 2003 in Elliott and Walker, 2005). Although many clinicians agree that sensory stimulation is beneficial for brain injured humans, the research that has been published so far, fails to determine the efficacy of these programmes in a convincing way. Some studies suggest a positive influence of sensory stimulation on recovery (Bontke, 1992; Carney et al., 1999; Dickinson et al., 2000; Giacino, 1996; Wilson and McMillan, 1993; Wilson and Powell, 1993). However, few firm conclusions can be drawn because of the lack of well-designed clinical studies (Giacino, 1996). Ethical and practical implications of including a no-treatment and well matched control group (Bontke, 1992; Giacino, 1996; Hall and Cope, 1995), and methodological problems like small sample sizes, poorly defined selection

criteria and lack of blinding of evaluators (Bontke, 1992), must always be taken into consideration, and have greatly limited the conclusions that can be drawn about the possible beneficial effect of sensory stimulation on recovery from coma.

The Rehabilitation Centre Leijpark (Tilburg, The Netherlands) uses an early Intensive Neurorehabilitation Programme (EINP) to children and young adults in a vegetative or minimally conscious state as a result of severe acquired brain damage. The aim of this treatment is to maximise a patient's ability to process and respond to stimuli and information of increasing variety and complexity. The rationale of the programme is based on theories as described above: providing structured sensory input and preventing deprivation in order to trigger the recovery processes as described above (See Appendix 1 for a detailed description of the Early Intensive Neurorehabilitation Programme, EINP). Eilander et al. (2005) showed that patients that participated in this programme had a more favourable outcome than predicted by 'The Multi-Society Task Force on Permanent Vegetative State' (1994b).

The present thesis does not address the question whether the EINP has an effect on final outcome in these patients, although all studies were in fact part of a larger research project aimed at evaluating the EINP (e.g., Eilander et al., 2007; Eilander et al., 2005). However, the very existence of this prolonged programme presented the opportunity to study this patient group in detail, using a longitudinal design and with measurement of various neurophysiologal parameters during the stimulation programme. All patients involved in the studies that make up the present thesis participated in the EINP. The studies involve about 50% of the Dutch children and young adults who were in a VS caused by severe acquired brain injury, for at least one month between January 2001 to January 2004 (Heutink et al., in press; see Appendix 7 for a detailed description of these patients).

Neurophysiological correlates of recovery to consciousness

At a clinical level, the recovery of consciousness is associated with the ability to communicate and to express goal-directed behaviour (Andrews, 1996; Giacino et al., 2004a). This in turn depends on various cognitive capabilities, such as sensory processing, arousal, motor behaviour, and language (Laureys et al., 2004a; Niedermeyer, 1999; Schiff and Plum, 2000; Vaitl et al., 2005; Young and Pigott, 1999). To examine how consciousness is altered and recovers after severe traumatic brain injury, these underlying components of consciousness, and their interaction with the environment can be studied. Consciousness can be altered in many ways (Vaitl et al., 2005); spontaneously (e.g. sleep, daydreaming), induced by psychological (e.g. meditation, relaxation) or pharmacological (e.g. anaesthesia, hallucinogens) means, and pathologically (e.g. coma, vegetative and minimally conscious states). A key assumption underlying the present work is the notion that these changes in consciousness are

paralleled by changes in the underlying cognitive processes. This is a reasonable assumption (e.g., Zeman, 2001), which allows studying the constituent cognitive processes underlying consciousness instead of consciousness as a whole, which might be difficult to define operationally.

These constituent cognitive processes underlying consciousness cannot be investigated without restrictions in unresponsive patients. Because the patients are uncommunicative, at least in the early stages of recovery, no tasks can be administered consistently throughout the whole recovery process, which require an understanding from the part of the patients, or a motor response. For this reason, the present studies are restricted to the study of arousal and sensory cognitive processes. Although this might seem to be a major restriction, it has the huge advantage that the same processes can be tracked throughout the whole recovery from coma to consciousness. Such studies are not available at the time of this writing, but should be able to provide a wealth of information on the recovery from coma. The procedures that are used are well described and documented in the literature. Therefore, accurate normative data from healthy populations are available, which can be used to compare the results in such a complex population such as vegetative and minimally conscious patients with.

Autonomic Nervous System: Arousal

The main function of the autonomic nervous system (ANS) is the adaptation of an organism's internal state to changes in the environment. The autonomic nervous system innervates every organ in the body, and accordingly, can modulate sensory, visceral, motor, and neuroendocrine functions. It functions independently (autonomously) and continuously, without conscious effort. The ANS is controlled by brain areas such as the anterior cingulate cortex, the insula, the amygdala, and the hippocampus (Critchley et al., 2002, 2003; Matthews et al., 2004). The neurotransmitters involved in autonomic activity comprise the cholinergic and noradrenergic pathways, and the nuclei releasing these neurotransmitters are the locus coeruleus and the basal nucleus of Meynert.

The autonomic nervous system can be subdivided into two major components: the sympathetic and the parasympathetic branches. The parasympathetic nervous system can be viewed as a restful or energy-conserving division of the autonomic nervous system, which is most active under ordinary, restful and digestive conditions. It also counterbalances the effects of the sympathetic part, and restores the body to a resting state following a stressful experience. The sympathetic nervous system activates body processes with the aim to create an attentive state in which one is able to 'fight and flight'. The sympathetic nervous system acts to increase output in certain emotional situations or extreme levels of exercise, and can be viewed as a mobilising and energy boosting division of the autonomic nervous system. In a healthy nervous system these branches of the autonomic nervous system are collaborating to maintain or create an optimal metabolic state, which is necessary given a particular action or environment. Therefore, the activity of the autonomic nervous system refers to the internal state of arousal,

vigilance, alertness, and even cognitive information processing. The functioning of the ANS can be assessed by measuring cardiovascular and electrodermal activity.

Cardovascular activity

Environmental input of different quality (e.g. emotional, cognitive stimulation) can activate different parts of the brain causing particular variations in heart beat. The brain areas involved in cardiovascular functioning are mostly located in the frontal cortex and include parts of the cingulated cortex, the insular cortex and the orbitofrontal cortex (Mesulam, 1983). Heart rate variability (HRV) can be used for measuring the function of both branches of the ANS, because the sympathetic and parasympathetic branches each make distinguishable frequency-specific contributions to the heart rate power spectrum (Mulder, 1992; see chapter 2 for our methods of spectral analyses of heart rate). Slow variations of the heart rate mainly reflect the influence of homeostatic control processes, mediated by the sympathetic branch of the ANS (Berntson et al., 1997). More rapid fluctuations reflect processes related to blood pressure, controlled predominantly, but not exclusively, by the sympathetic branch of the ANS (Akselrod et al., 1981). Very fast fluctuations are related to respiratory activity, primarily controlled by the parasympathetic branch of the ANS (Akselrod et al., 1981; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). In addition, the balance between both branches of the ANS can be examined using HRV (Malliani et al., 1998; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). This so-called sympathovagal balance reflects the overall state of the autonomic nervous system resulting from both the sympathetic and parasympathetic influences (Eckberg, 1997). Together, these measures will be used to examine the state of arousal in the patients of the present studies.

Electrodermal activity

Electrodermal activity (EDA) is thought to reflect attention to new information in the environment, and some elementary forms of learning (habituation – decreasing reaction intensity with repeated stimulation), memory storage and retrieval (Boucsein, 1993). Although not fully understood, electrodermal activity (EDA) can be elicited by at least three different, but interconnected central pathways: a premotor cortical-spinal system, a limbic-hypothalamic system, and pathways involving the reticular formation (Dawson et al., 2000). Different environmental stimuli can activate different parts of the brain to cause electrodermal reactivity to occur. The ipsilateral limbic system primarily controls electrodermal activity in response to emotional and affective situations, whereas the contralateral system is critical in controlling electrodermal activity during orienting and cognition.

Electrodermal activity is highly influenced by the sympathetic part of the autonomic nervous system. Human sweat glands have predominately sympathetic cholinergic innervation

from sudomotor fibres originating in the sympathetic chain, and some adrenergic fibres also exist in close proximity (Shields, 1983).

Central nervous system: perceptual and cognitive processes

The electroencephalogram (EEG) represents a record of the spontaneous electrical activity of the brain, measured from electrodes fixed at standard locations on the scalp. Event Related Potentials (ERPs) are fragments of EEG activity that have a fixed temporal relation to some event. This event can either be external, as in the case of the presentation of a stimulus or the production of a response, but it can also be internal, as in a cognitive event such as the detection of change or language production. ERPs related to external events are also called exogenous components, or Evoked Potentials (EPs); those related to internal events are termed endogenous potentials, or cognitive ERPs.

Evoked Potentials: elementary perceptual processing

EPs can be evoked by applying a stimulus via any of the sensory pathways. Auditory, somatosensory, and visual stimuli are commonly used for clinical studies.

Brain stem auditory evoked potentials (BAEPs) measure the function of the auditory nerve and auditory pathways in the brain stem. BAEPs are useful in estimating or aiding in the assessment of hearing loss. BAEPs predominantly activate the pathways in the brainstem ipsilateral to the side of the stimulus (click stimulation). The BAEP-component exists of five negative peaks (I – V) all corresponding to a specific part of the auditory pathway (see table 3 for the underlying structures of the peaks). In severe hearing loss, all waveforms may be delayed, wave I may be absent with waves II through V delayed, or all waveforms may be absent.

Somatosensory Evoked Potentials (SSEPs) consist of a series of waves that reflect sequential activation of neural structures along the somatosensory pathways following electrical stimulation of peripheral nerves. In clinical practice, SSEPs are elicited typically by stimulation of the median nerve at the wrist, the common peroneal nerve at the knee, and/or the posterior tibial nerve at the ankle, and recorded from electrodes placed over the scalp, spine, and peripheral nerves. The SSEP exists of short- and long-latency components (see table 3 for the underlying structures). The long-latency components are referred to as cortical SSEPs (cSSEP). Abnormal SSEPs can result from dysfunction at the level of the peripheral nerve, plexus, spinal root, spinal cord, brain stem, thalamocortical projections, or primary somatosensory cortex.

Visual Evoked Potentials (VEPs) probe the function of the visual pathway from the retina to the occipital cortex. They reflect the activity of the visual pathways from the optic nerve though the optic chiasm, and optic radiations to the peristriate and striate occipital cortex. VEPs consists of three negative waves, alternated with three positive waves. See table 3 for the

underlying structures of the peaks. Both the nomenclature of Cigánek (1961) and Odom et al. (2004) are presented.

Table 3 The relation between EP components and brain structures

BAEPs	**I** cranial nerve	**II** cochlear nucleus and cranial nerve		**III** (ipsilateral) superior olivary nucleus		**IV** lateral lemniscus	*V* inferior colliculus	
	P14	**N20**	**P20**	**P25 (22)**	**P27**	**N30**	**P45**	**N60**
SSEPs	medial lemniscus	primary somatosensory cortex (parietal)	primary motor cortex (frontal)	vertex (central)	primary sensory cortex (parietal)	primary motor cortex (frontal)	rolandic fissure peri-rolandic region (pre- and postcentral gyri) (central)	secondary somatosensory cortex (SII) parieto-rolandic operculum fronto-central
Flash VEPs	**P1** optic nerve	**N2/III** optic chiasm	**P2** Vertex (central)	**N3/VII** peristriate and striate occipital cortex				

Cognitive Event Related Potentials: cognitive processing

Mismatch Negativity

The Mismatch Negativity (MMN) is a brain wave that detects auditory deviance in a regular sequence of tones. The MMN can occur in the absence of attention, and has been associated with some form of preattentive or sensory memory. The MMN was first described by Näätänen (1978). Two classes of auditory stimuli are presented, which differ in the probability of presentation. The person's attention is not devoted to the series of tones but instead to another task, such as reading a book. To derive the MMN, the average waveform elicited by the standard (frequent) stimuli is subtracted from that of the deviant (rare) stimuli. This subtraction yields a negative component with a peak latency of 100-200 ms. This component is usually largest at frontal and central electrode sites (Fabiani et al., 2000). Magnetoencephalographic recordings (Alho et al., 1998), and topographic event related potential study (Giard et al., 1990) revealed that MMN originates from the superior and middle temporal gyri and some prefrontal areas.

The MMN is suggested to reflect the comparison of the current input with the neutral trace of prior stimulation (Näätänen, 1990). Although the MMN is elicited by preattentive monitoring of a change in an unattended stimulus sequence, it is suggested to be a sign of the activation of an attention-switching mechanism (Näätänen, 1990). ERPs with a longer latency, such as the P300 are thought to reflect processes necessary for conscious sensory experience,

even though earlier processes may be sufficient for detecting a stimulus without being aware of it (e.g., Libet et al, 1967 in Näätänen, 1990).

P300

The 'classical' P300 exists of a late positive component which is elicited by task-relevant oddball stimuli and is maximum at posterior, parietal scalp locations (Sutton, 1965). It has been suggested that the P300 results from the summation of activity from multiple generators located in widespread cortical and possibly subcortical areas. The exact neural origin is uncertain, however, but the effects on the amplitude and latency of P300 are well studied. The amplitude is sensitive to stimulus probability (Donchin et al., 1997), and is related to the processing recourses demanded by a particular task (Donchin, Kramer, and Wickens, 1986, in Fabiani et al., 2000). P300 latency appears to reflect stimulus evaluation and categorization time (Donchin, 1979, in Fabiani et al., 2000). As categorization becomes more difficult, P300 latency becomes longer.

A distinction can be made between the anterior scalp distributed oddball response, termed P3a, which reflects the orienting response, and the posterior, parietal scalp distributed oddball response, termed P3b, which reflects the more cognitive equivalent of the oddball response (Rugg & Coles, 1995).

According to Polich and Kok (1995) the P300 can be considered as activity of the central nervous system involved in processing of new information when attention is engaged to update memory representations. Thus, the P300 is interpreted as a manifestation of attention allocation and context updating.

Neurophysiological measures in the acute phase

In the acute phase, the depth of coma is usually determined by means of the Glasgow Coma Scale (Teasdale and Jennett, 1974). Complementary diagnostic investigation by means of neurophysiological assessment is often carried out, but this is intended mainly to diagnose the severity and extent of the brain damage (haemorrhage, oedema, diffuse swelling, intracranial pressure, epileptic seizures, et cetera). In addition, neurophysiological measures in the acute phase are sometimes used to predict the clinical outcome (Fischer et al., 2004; Guérit et al., 1993; Guérit et al., 1999; Kane et al., 2000; Luauté et al., 2005; Wardlaw et al., 2002). Using these methods, it has been predicted successfully whether a patient survives and awakens from coma to full consciousness, or whether a patient dies or shifts into a VS (Amantini et al., 2005; Fischer et al., 2004; Guérit et al., 1993; Mazzini et al., 2001; Wang et al., 2004).

Heart rate variability is very low in comatose patients in the acute phase (Lowensohn et al., 1977). An increase in the sympathovagal balance has been found in patients who had recovered from a comatose state (Hildebrandt et al., 1998). Higher sympathetic and lower parasympathetic activity were paired with better scores on the GCS (8–10). Recently, Su et al.

(2005) compared HRV with severity of brain damage. In the more severely brain-damaged patient groups both sympathetic and parasympathetic activity were lower in comparison to less severely brain damaged patient groups, and in comparison to a healthy norm group. In brain dead patients, near-zero levels of heart rate power spectra were found (Goldstein et al., 1998).

Exogenous evoked potentials are also often studied in the acute phase, both to examine sensory functions, and to draw conclusions on the functioning of the brainstem and midbrain. Mostly, Brainstem Auditory Evoked Potentials (BAEPs) and Somatosensory Evoked Potentials (SSEPs) have been studied. Some studies also examined Visual Evoked Potentials (VEPs). Greenberg et al. (1977a; 1977b) examined BAEPs, SSEPs and VEPs serially in comatose patients with different recovery patterns. They observed that the presence of the waves with a longer latency depended on the patient's level of consciousness, and they therefore concluded that the later waves may prove to be useful determinants of the depth of coma (Greenberg et al., 1977a). EPs in comatose patients have been found to differ from healthy subjects (Rappaport et al., 1981). Patients' latencies were significantly longer, and their amplitudes were significantly smaller as compared with the healthy subjects.

Many studies have demonstrated the usefulness of EPs in predicting mortality and outcome in comatose patients (Amantini et al., 2005; Fischer et al., 2004; Guérit et al., 1993; Mazzini et al., 2001; Wang et al., 2004). A bad outcome is likely to follow when brainstem auditory and somatosensory evoked potentials (BAEPs and SSEPs) fail to appear in the acute phase after severe brain damage (Wang et al., 2004). Especially SSEPs measured in the first week post-injury seem to be most useful to predict a poor outcome (Zandbergen et al., 1998). Guérit et al. (1993; 1994; 2000; 2005a) developed a method using BAEP, SSEP and VEP morphology, to classify brain injured patients based on severity of brain damage. Different patterns were associated with various anoxic and traumatic pathologies. According to Guérit's system, patients can be classified based on their brainstem conduction (Index of Brainstem Conduction, IBSC), and on their global cortical functioning (Index of Global Cortical Function, IGCF), and their neurological outcome can be predicted. Especially the IGCF, which is mainly determined by long latency SSEPs and VEPs, was found to be of importance to predict a favourable outcome. The latter finding emphasizes the importance of VEPs, which are not used very often in studies in the acute phase.

The existence of cognitive endogenous ERPs, e.g., P300 and MMN, is of great predictive value for good outcome (Fischer et al., 2004; Guérit, 2000; Kane et al., 2000; Luauté et al., 2005; Morlet et al., 2000). In the study of Fisher et al. (2004), none of the patients in whom MMN was present remained vegetative. However, its value to predict bad outcome is low (Fischer et al., 1999). Also, the presence of a P300 is often associated with the awakening from (non)traumatic coma (Guérit, 2000; Guérit et al., 1999; Kane et al., 2000). The presence of a P300 in the acute phase is a sign of a good prognosis, sometimes even 100% (Guérit et al., 1999), but no conclusions can be drawn from its absence. Groups of patients with good and with bad outcome have been found, and neither group showed a P300 in the acute phase.

Neurophysiological measures in the post-acute phase

In the post-acute phase, observation scales are also used, examining the recovery to consciousness by observing behavioural skills, such as the Western Neuro Sensory Stimulation Profile (Ansell et al., 1989), the Rancho Los Amigos Scale (Hagen et al., 1972), the JFK Coma Recovery Scale-revised (Giacino et al., 2004), and the Disability Rating Scale (Rappaport et al., 1982). Yet during this post-acute phase neurophysiological assessment is not always considered to be important. However, new insights have shown possible information processing in vegetative and minimally conscious patients. Recently, neurophysiological reactivity has been demonstrated in VS and MCS using ERPs (Kotchoubey et al., 2002; 2005; Neumann and Kotchoubey, 2004), and using functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET; Boly et al., 2004; Jong et al., 1997; Laureys et al., 2000a; 2004a; 2004b; Owen et al., 2002; 2005; Schiff et al., 2002; 2005). Surprisingly, there are only a few studies that examined electrophysiological measures such as heart rate, electrodermal activity, or brain potentials in the post-acute phase.

Studies in which endogenous ERPs were examined revealed that they can be evoked sometimes in the vegetative and minimally conscious states (Guérit, 2005b; Kotchoubey et al., 2005), especially when salient stimuli were used, such as the patients name (Laureys et al., 2004b), speech (Kotchoubey et al., 2001), and musical notes (Jones et al., 2000; Kotchoubey et al., 2001; 2003). No large differences were found between vegetative and minimally conscious patients. Thus, it appears that external stimuli (such as sounds) can provoke cortical activity in the VS (Kotchoubey et al., 2005; Laureys et al., 2000a; Owen et al., 2005; Schiff et al., 2002). However, fMRI studies suggested that this activity is often limited to isolated activity in certain 'cortical islands' (Menon et al., 1998; Plum et al., 1998; Schiff et al., 1999; 2002; Schiff and Plum, 1999), which are not integrated in the entire network of information processing. In some case studies brain activity has been found with the accompanying behavioural responses. However, this behaviour was completely unrelated to the environmental context (Schiff et al., 1999).

PET scanning demonstrated resting brain metabolism in subcortical structures in the VS to be lower than in sleep, not so low as in coma (Rudolf, 2000 in Vaitl et al., 2005). Vegetative patients show a systematic impairment of metabolism in the polymodal associative cortices (among which bilateral prefrontal regions) (Laureys et al., 2004a). Brain metabolism in the VS is reduced by 50% compared to a healthy brain (Laureys et al., 2002a; Laureys et al., 1999). In addition, in the VS brain metabolism of different brain areas is unrelated, presumably because of the disconnection between these areas (Boly et al., 2004; 2005; Laureys et al., 1999; 2002a). Postmortem research showed that in the VS often a structurally normal cortex was intact (Adams et al., 2000), however, without any connection to other areas like the thalamus.

Resting brain metabolism in the MCS is decreased to values slightly higher, but comparable to those observed in the VS (Boly et al., 2004; Laureys et al., 2004b). In minimally conscious patients, corticocortical functional connectivity is more active, relative to the VS,

between the auditory cortex and a large network of temporal and prefrontal cortices. In the MCS the associative brain areas (secondary and tertiary) are active in response to external stimulation such as sound or pain (Boly et al., 2005). These areas are necessary for the conscious perception of stimuli (Baars et al., 2003). In some studies, it was found that brain activity in the MCS in response to sound and pain stimulation was indistinguishable from the activity found in a healthy control group (Laureys et al., 2002b; Schiff et al., 2005).

Some case studies

Recently, some remarkable case studies have been described that shed new light on the assessment of consciousness, and on recovery processes. Laureys et al. (1999; 2000b; 2006) described some case studies of recovery from to VS to consciousness, and identified long-range cortico-cortical (between midline-posterior and latero-frontal areas) and cortico-thalamic (between midline-posterior cortices and non-specific thalamic nuclei) disconnections in a cohort of VS patients. The rare cases that recovered showed a partial functional restoration of these connections.

A recent case study of Owen et al. (2006) attempted to reveal the possibly present *conscious* information processing in an unresponsive patient using fMRI. In this study a vegetative woman was asked to imagine herself to play tennis and to move around in her own house. During these tasks the woman showed identical brain activity when compared to healthy controls. The authors concluded that this woman 'made the decision to cooperate', which means that it was a conscious act, without any behavioural sign. We cannot be completely sure whether this patient was really fully conscious, because we cannot know the quality of this woman's experience (Owen in Hopkin, 2006). More importantly, we can never be sure whether someone is *not* conscious only because there is no behavioural sign of consciousness.

Nevertheless, the case study of Owen et al. (2006) raises some important questions. The study may suggest that all vegetative patients can be considered internally conscious. If that is indeed the case, the VS resembles the "locked-in syndrome": a condition in which a patient is conscious and awake, but cannot move or communicate due to complete paralysis of nearly all voluntary muscles in the body, but can communicate by eye or eyelid movements (Laureys et al., 2004a). However, this is probably not the case; the woman in question was examined immediately before showing signs of recovery (Laureys in Hopkin, 2006). It is not known whether she would have shown the same brain activity two weeks earlier, or whether other vegetative patients would have shown the same brain reactivity. It may be that only patients who will finally recover from the VS will show neurophysiological reactions resembling healthy controls. This emphasises the necessity to study more patients at different time points during their recovery.

A second case study describes the neural correlates of the 'miraculous awakening' of a man who was in the MCS for 19 years (Voss et al., 2006). In June 2003 it was announced that

this man had awakened after 19 years of 'coma'. He was then able to verbally express himself; therefore, he no longer fulfilled the criteria of the minimally conscious state: he 'awoke' from the minimally conscious state to consciousness. Diffusion Tension Imaging (DTI: imaging of white matter where the location, orientation, and anisotropy of the tracts can be measured) revealed that cells in the relatively undamaged areas had formed new axons, the long nerve fibres that transmit messages between neurons. Probably, his brain was methodically rebuilding the white-matter infrastructure necessary for him to interact with the outside world. His brain may have been seeking out new pathways to re-establish functional connections to areas involved in speech and motor control (Voss et al., 2006).

Although this man was already able to respond to questions with grunts, and by blinking his eyes, a few years before he started speaking (Wijdicks, 2006), the moment at which he was able to verbally express himself was probably worth the announcement of his 'awakening'. Probably as a result of clinicians being obliged to reduce reality to a binary condition (Laureys in Hopkin, 2006). Was he not already conscious before he started speaking? Besides the necessity of studies in which the same patients are followed longitudinally, it is important to take into account the "greyzones" between the vegetative and minimally conscious state, and the small gradations within the diagnoses. Neurophysiological measures may give some clarity on these borders of the diagnoses.

These case studies show the importance of seeking (objective) measures to study the recovery of consciousness. Complementary to observation methods, neurophysiological reactivity can uncover diagnostic errors. In addition, we can learn more about the brain's capacities to recover from severe damage, even after such a long time.

Interim conclusions

Neurophysiological reactivity appears to differ between patients with different diagnoses: e.g. between patients with different scores on the GCS in the acute phase, and between the VS and the MCS in patients in the post-acute phase. In addition, the neurophysiological reactivity of patients in all of these groups differs from that of healthy subjects. Imaging studies suggest that the differences between the VS and the MCS may particularly relate to a better communication between subcortical and cortical areas, and the integration and communication between primary, secondary and tertiary areas in MCS patients.

Neurophysiological parameters have been studied in the acute phase, and have been shown to be of predictive value. However, neurophysiological reactivity in the post-acute phase, during the recovery from the VS to consciousness is hardly investigated. In the post-acute phase, most of the studies only describe individual cases. Patients in the post-acute phase are often spread out over rehabilitation centres, nursing homes, and common households, where the equipment for such measurements is often lacking. In the studies described in this thesis

the patients all remained at a single location for a longer period, which made a longitudinal, prospective within-subject study possible.

Organization of the thesis

In **Chapter 2** a methodological overview is presented of the procedures used for measuring the level of consciousness in the present patients, the techniques for recording the electrophysiological signals, and the methods for handling the recorded data, including the statistical analysis.

Chapter 3 presents the results on the evoked potentials: Brainstem Auditory Evoked Potentials, Somatosensory Evoked Potentials and Visual Evoked Potentials.

Chapter 4 presents the results obtained in the autonomic measures, heart rate variability and electrodermal activity. This study has been published in *Clinical Neurophysiology*, 117 (2006) as " Autonomic reactivity to sensory stimulation is related to consciousness level after severe traumatic brain injury", authored by Wijnen VJM, Heutink M, van Boxtel GJM, Eilander HJ, de Gelder B.

In **Chapter 5** the results on the mismatch negativity are presented. This study has been published in *Clinical Neurophysiology*, 118 (2007) as "Mismatch negativity predicts recovery from the vegetative state", authored by Wijnen VJM, van Boxtel GJM, Eilander HJ, de Gelder B.

Chapter 6 presents the results on the classical auditory oddball paradigm: P300.

Finally, a description of all patients is given in Appendix 7. Because the same patient numbers were used throughout the thesis, a comparison of the different electrophysiological measures at an individual level can be extracted from the data distributed throughout the thesis.

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Chapter 2

Methods

The current chapter describes the methods used in the different studies that make up the current thesis. The research described in this thesis was part of a project aimed at evaluating the effects of the Early Intensive Neurorehabilitation Programme (EINP) in children and young adults in a vegetative or minimally conscious state (see Appendix 1 for a detailed description of the EINP). Various aspects of the possible effects of the EINP were evaluated in the project, including the course of recovery to consciousness and the final outcome in terms of behavioural and clinical measures; functional possibilities or disabilities; quality of life; and the effects on the grieving process of the next of kin. In addition, ethical aspects regarding the choices about the treatment were studied, such as its start, intensity, contents, and its duration. The total project thus consisted of six parts: an extensive literature study, a retrospective outcome study, a prospective cohort outcome study, a medical-ethical study, a study of the relevant aspects in close relatives, and a prospective neurophysiological study. The current thesis describes the results of the ***prospective neurophysiological study.*** Its aim was not to evaluate the effects of the EINP per se, but to increase the understanding of the course of recovery from the vegetative state to consciousness, by relating behavioural observation methods with neurophysiological parameters.

The prospective neurophysiological study consisted of two parts that were separated in time, due to the availability of the recording equipment. As a result, the number of participants varied over studies.

Study 1

In the first study autonomic measures (heart rate and skin conductance) were recorded during the administration of structured sensory stimulation with the Western Neuro Sensory Stimulation Profile (WNSSP; Ansell et al., 1989). Behavioural reactions were assessed using the Post Acute Level of Consciousness scale (PALOC-s; Eilander et al., submitted), the Disability Rating Scale (DRS; Rappaport et al., 1982), and the WNSSP. This study took place between January 2001 and May 2002.

Study 2

In the second study, the equipment for recording brain activity (BioSemi) was available, and various ERP tasks were administered. The behavioural observations were performed using the PALOC-s. Study 2 took place between November 2002 and January 2004.

Appendix A (at the end of this chapter) presents the overall research protocol, which was pursued for each patient from the admission up to the discharge of the EINP. Appendix B (at the end of this chapter) presents a summary of the tasks used in both studies.

Participants

Patients

In total, twenty-eight patients with severe brain injury who were admitted to the EINP between January 2001 and January 2004 were included in the studies. The studies encompass about 50% of the Dutch children and young adults who were in the VS caused by severe acquired brain injury for at least one month, between January 2001 and January 2004 (Heutink et al., in press). Nineteen patients (67.9%) were male. For the total group, the age at the time of the injury ranged from 6 to 25.5 years (M = 19.4 years; SD = 4.7 years). The average period between the time of the injury and the admission to the EINP was 71 days (SD = 35 days, range 31 - 198 days). The duration of the patients' participation in the program depended on their recovery rate, and ranged from 34 to 195 days (M = 105 days; SD = 37 days). The major cause of the injury was the involvement in a traffic accident (85.7%; see table 1).

Appendix 7 describes all patients individually. In addition, the individual recovery track of each patient is presented. If available, a representative Computerised Tomographic scan (CT-scan) is displayed. Patient 1 to 16 participated in study 1, and patient 17 to 28 participated in study 2. The patient numbers listed in the following experimental chapters refer to the patient numbers in Appendix 7. In this way, the characteristics of the patient group involved in a particular experiment is always traceable. Appendix 7 also presents a table with a short summary of the patients' characteristics.

Healthy control group

A healthy control group was recruited for study 2. It consisted of 16 persons, matched for mean age (p = 0.6) and gender (56% were male).

All the patients and the norm group participated in the studies following informed consent given by one of the parents or by a legal representation (all the patients and the norm group when aged under 16 years), or by themselves (norm group aged over 16). The study has been approved by a medical ethics committee (METTOP).

Clinical assessment

Several observation scales were used for the clinical assessment of the patients. For short-term progress the PALOC-s was used as a measure of the Level of Consciousness (LoC). The Disability Rating Scale (DRS) and the WNSSP were used to measure changes in arousal and consciousness, and in cognitive, functional, and psychosocial domains. For the long-term outcome the DRS in categories (DRScat) and the Glasgow Outcome Scale Extended (GOSE;

Wilson et al., 1998) were used. In addition, CT-scans were collected and scored according to the classification of Marshall (Marshall et al., 1991).

Observation Scales: Short-Term Progress

Post Acute Level of Conscious Scale (PALOC-s): Level of Consciousness (LoC)

For the assessment of the Level of Consciousness (LoC), a categorisation was used based on the literature about the terminology and the definitions described by the 'International Working Party Report on the Vegetative State' (Andrews, 1996) and the Aspen Neurobehavioural Conference (Giacino et al., 1997). The categorisation describes eight hierarchical levels: Coma (1), Vegetative State hyporesponsive (2), Vegetative State reflexive state (3), Vegetative State high (re-)active (4), Minimally Conscious State transitional state (5), Minimally Conscious State inconsistent reactions (6), Minimally Conscious State consistent reactions (7), and Consciousness (8). See Appendix 3 for the classification scheme in detail.

Validation of this scale was part of the overall research project. Preliminarily examination of this observation scale showed high reliability and validity. The inter-observer correlations on LoC varied between 0.82 and 0.95, and the intra-observer correlations varied between 0.95 and 0.96. The correlations with the WNSSP varied between 0.88 and 0.93, and with the DRS between 0.75 and 0.88 (Eilander et al., submitted).

Western Neuro Sensory Stimulation Profile (WNSSP)

Cognitive and communicative functioning was assessed using the Western Neuro Sensory Stimulation Profile (WNSSP; Ansell et al., 1989). The WNSSP was specifically developed to assess the cognitive state and communicative performance in severely impaired head-injured patients. The WNSSP consists of 33 items that assess a patient's arousal and attention, expressive communication, and response to auditory, visual, tactile, and olfactory stimulation. Six subscales (arousal and attention, auditory comprehension, visual comprehension, visual tracking, object manipulation, and expressive communication) and four additional observations (response to sound, speech, smell, and touch) have been delineated, which assess specific aspects of a patient's behaviour and provide a means for evaluating a patient's pattern of response. The total score ranged from 0 to 113 (higher scores denote better performance on the scale). See Appendix 4 for a detailed description of the WNSSP.

Disability Rating Scale (DRS)

The Disability Rating Scale (DRS; Rappaport et al., 1982) was used to assess changes in arousal and consciousness, and in cognitive, functional, and psychosocial domains. The DRS is a quantitative instrument with a continuous 30-point scale for assessing the disability of severe TBI patients. The scale consists of eight items arranged over four categories: 1) arousability, awareness, and responsivity (similar to the GCS) 2) cognitive ability for self-care activities, 3)

level of dependency, and 4) psychosocial adaptability. Only the total DRS score was used in the present studies. The lower the total DRS score the fewer the disabilities, ranging from death (score 30) to no disability (score 0). This, higher scores denote better outcome on the DRS. See Appendix 5 for a detailed description of the DRS.

Observation scales: Long-Term Outcome

To determine the long-term functional outcome, the DRS (Rappaport et al., 1982), as well as the Glasgow Outcome Scale Extended (GOSE; Wilson et al., 1998) were used.

To make the two scales more comparable, the DRS was reduced to 8 categories and is referred to as DRScat (Rappaport et al., 1982): 1=death (score 30), 2=vegetative state (score 22-29), 3=extremely severe disabled (score 17-21), 4=severely disabled (score 12-16), 5=moderately severe disabled (score 7-11), 6=moderately disabled (score 4-6), 7=mildly to partially disabled (score 1-3), and 8=no disability (score 0). See Appendix 5 for a description of the DRScat.

The GOSE is an extension of the Glasgow Outcome Scale (GOS; Jennett et al., 1981). The GOSE is a one-item rating scale including eight outcome categories (from 'dead' to 'upper good recovery') and can be administered through a structured interview. Compared to the GOS, the GOSE has been shown to be more sensitive to changes in mild to moderate TBI (Wilson et al., 1998). The GOSE consists of eight items: 1=death, 2=vegetative state, 3=lower severely disabled, 4=upper severely disabled, 5=lower moderately disabled, 6=upper moderately disabled, 7=lower good recovery, 8=upper good recovery. The GOSE was administered in a structured interview as proposed by Wilson et al. (1998). See Appendix 6 for a detailed description of the GOSE.

Classification of initial CT scans

A classification of the initial CT scans of each patient was carried out by a neurosurgeon, according to the guidelines proposed by Marshall et al. (1991). In this classification a category of 1 to 5 is allocated to the scan (Table 1). The categories are based on the following scan features: overall scan appearance, focal lesions (subdural, extradural) contusions, parenchymal lesions (small, shearing), subarachnoid haemorrhages (basal, cortical, tentorial), intraventricular haemhorrhages, significantly depressed fractures, midline shift (mm), basal cisterns absent or compressed, third ventricle compressed, contralateral ventricle dilated, hydrochephalus, intracranial air, and ischemia. See Appendix 7 for individual scores of the CT-scans.

Table 1 CT-classification according to Marshall et al. (1991)

Score	Category	Details
1.	Diffuse injury	NVP: no visible intracranial pathology on CT scan.
2.	Diffuse injury	Cisterns present with shift 0,5 cc and/or lesion density present, but not high or mixed density lesion > 25 cc. May include bone fragments and foreign bodies.
3.	Diffuse injury with swelling	Cisterns compressed or absent, shift 0 - 5, no high or mixed density lesion > 25 cc
4.	Diffuse injury with shift	Shift > 5 mm; no high or mixed density lesion > 25 cc
5.	Mass lesions	High or mixed density lesion > 25 cc

Neurophysiological assessments: recording and analysis

Autonomic Nervous System

Heart rate

Heart rate was measured using three disposable Ag-AgCl electrodes (with a contact area of 15 mm) placed on the sternum and the precordial position V6 (Mulder, 1992). The reference electrode was placed under the right clavicle. The inter beat intervals (IBIs) were stored on a personal computer, using an IBI-trigger which detected the R-waves of each heartbeat with a temporal resolution of 1 ms.

Recordings were divided into three epochs, representing the first resting period, the stimulation period with the WNSSP, and the second resting period. Artefacts in the IBI series were detected by outlier analysis based on the mean and standard deviation of the series (Berntson et al., 1995). These parameters were adjusted for each patient (and each measurement) individually, and based on visual inspection of the whole series. Outliers were deleted from the original series and replaced by values resulting from the application of a cubic spline function. IBIs were then converted to a real-time base at 2 Hz, detrended, tapered with a 10 percent cosine window, and then transformed into the frequency domain (Berntson et al., 1995).

Mean values for the power density in absolute values of power (milliseconds squared) were calculated separately for low frequency (LF; ≤ 0.04 Hz), middle frequency (MF; 0.04 – 0.15 Hz), and high frequency (HF; 0.15 – 0.40 Hz) band , and total power (TP; ≤ 0.40) was computed as well. Because the raw power values are influenced by the length of the data series, which varied in our administration of the WNSSP, we only report on the power in normalised units (n.u.), separately for the MF (MFn.u.: MF / [TP-LF] x 100) and HF (HFn.u.: HF /

[TP-LF] x 100). Sympathovagal balance was calculated as MF/HF (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996) .

Electrodermal activity

Skin Conductance Level was measured in order to examine tonic changes in electrodermal activity (see Boucsein, 1993). Skin conductance, expressed in microSiemens (μS), was recorded from the thenar and hypothenar eminences of the non-dominant hand. Two Ag-AgCl skin electrodes (contact area of 8 mm) were attached, filled with an electrolyte consisting of 0.05 M NaCl in a unibase cream medium (Boucsein, 1993). An electric circuit applied a constant voltage of 0.5 V. Raw skin conductance values were digitised at a rate of 10 Hz, and stored on a personal computer.

Skin conductance level (SCL) was determined by averaging all data samples of each of the three intervals. This value was referred to a calibrated baseline, which was set at the start of each measurement. Voltages were converted to microSiemens (μS = R [calibrated voltage / averaged voltage] * 1000kOhm).

Electroencephalographic studies

The electroencephalographic studies were inspired by the 'Recommendations for the practice of clinical neurophysiology: guidelines of the International Federation of Clinical Neurophysiology' (1999). See Appendix B at the end of this chapter for a summary of the recording features.

Overall neurophysiological recordings

The equipment used for the electroencephalographical recording (BioSemi ActiveTwo, The Netherlands) was approved on safety by a Metron QA-90 Safety tester in the Tweesteden Hospital (The Netherlands). The recording system featured actively shielded pin-electrodes, eliminating problems with high electrode impedances, and cable shielding. The system has a high Common Mode Rejection Ratio (> 80 dB). The electrodes were placed using an EEG-headcap and electrode gel (Parker Signa) according to the 10/20 system, at F3, Fz, F4, C3, Cz, C4, Pz, and Oz, referenced to linked mastoids. Horizontal EOG was recorded from two electrodes placed at the outer canthi of both eyes. Vertical EOG was recorded from electrodes placed on the infraorbital and supraorbital regions of the two eyes in line with the pupil. EOG artefacts were corrected using a regression procedure (Gratton et al., 1983). The recordings of Brainstem Auditory, Somatosensory, and Visual Evoked potentials were done with a sampling rate of 8 kHz. The recordings of Mismatch Negativity and P300 were done with a sampling rate of 2 kHz.

Brainstem Auditory Evoked Potentials (BAEPs)

The auditory stimuli were 2000 clicks, with an intensity of 70 dB SPL, a duration of 10 µsec, and a frequency of 11 Hz. The tones were delivered both binaurally and unilaterally through insert earphones in three sessions. EEG signals were band-pass filtered (100 – 3000 Hz, 48 dB/octave). The raw data were segmented into 2000 epochs, including a 5 ms prestimulus baseline, and a 10 ms poststimulus response time. BAEPs were examined on Cz. Different references were used for uni- and bilateral measurements: bilateral measurements were analysed both with left and right mastoids as a reference (M1 or M2). For the unilateral sound presentations the mastoid ipsilateral to the stimulated ear was used. The raw data were segmented into 2000 epochs, including a 5 ms prestimulus baseline, and a 10 ms poststimulus response time. Peak I, III and V were examined on their presence, and, if present, on their interpeak latencies (see table 3 for the underlying structures, chapter 1).

Somatosensory Evoked Potentials (SSEPs)

The somatosensory stimuli were 2000 electrical pulses, with an intensity of maximal 20 mA, a duration of 10 µsec, and a frequency of 3 Hz. The stimuli were delivered unilaterally to the median nerve of the left and right wrist in two sessions. EEG signals were band-pass filtered (3 - 200 Hz, 48 dB/octave). The raw data were segmented into 2000 epochs, including a 10 ms prestimulus baseline, and a 100 ms poststimulus response time. Depending on the stimulated wrist and the components of interest, SSEPs were examined on Pz, C3, C4, Fz, F3, and F4. The mastoid ipsilateral to the stimulated wrist was used as reference.

The SSEP exists of short- and long-latency components (see table 3 for the underlying structures, chapter 1). All components were examined on their presence.

Visual Evoked Potentials (VEPs)

The visual stimuli were 300 white flashlights presented with a frequency of 1Hz. The flashlights were presented bilateral using a 'White Flash Nihon Kohden model EEG-4314 F/G'. The lamp was in distance of about 30cm of the participant. EEG signals were band-pass filtered (3 – 100, 48 dB/octave). The raw data were segmented into 300 epochs, including a 5ms prestimulus baseline, and a 500ms poststimulus response time. Peaks amplitudes and latencies were examined on Oz with a reference at Fz.

The VEPs exists of 3 negative waves, alternated with 3 positive waves: N1, P1, N2, P2, N3, P3. See table 3 (Chapter 1) for the underlying structures of the peaks, in which both the nomenclature of Cigánek (1961) and Odom et al. (2004) are presented.

The long-latency peaks N2 (III), P2 and N3 (VII) were examined on their presence, and, if present, on interpeak latency, and peak-to-peak amplitudes: N2 – P2 and P2 – N3.

MMN data acquisition and analysis

The presented stimuli were 1500 pure tones of 1000 Hz (85%, standard) and 1500 Hz (15%, deviant), with an intensity of 70 dB SPL and duration of 75 ms (rise and fall time 10 ms), delivered binaurally through insert earphones. The fixed interstimulus interval was 500 ms.

EEG signals were band-pass filtered (0.15-30Hz, 48 dB/octave). The raw data were segmented into 1500 epochs, including a 100 ms prestimulus baseline. Epochs with an amplitude change exceeding ±100 μV at any channel were automatically rejected. ERPs were averaged separately for the standards and deviants. The ERP to standards included the responses to those standards which immediately followed deviants.

After averaging the standard and deviant responses for each measurement and subject the ERPs were filtered between 3 – 30 Hz (Fischer et al., 1999; Morlet et al., 2000). For each measurement in every subject it was visually inspected whether the N1 was present both in averaged standard and deviant responses. Difference waveforms were then computed by subtracting the averaged ERP elicited by the standard from that of the deviant, and these were filtered between 3 – 8 Hz (Fischer et al., 1999; Morlet et al., 2000). For each measurement in every subject, MMN was defined as being any negativity differing from zero level within the time window of 100 – 300 ms.

P300

The stimuli were 375 pure tones of 1000 Hz (80%, standard) and 2000 Hz (20%, deviant), with an intensity of 70 dB SPL and a duration of 75 ms (rise- and fall time 10 ms). The tones were delivered binaurally through insert earphones. A random inter stimulus interval of 1000 to 2000 ms was used (steps of 1 ms; rectangular distribution). EEG signals were band-pass filtered off-line (0.15 – 30 Hz, 48 dB/octave). The raw data were segmented into 375 epochs, including a 100-ms prestimulus baseline. Epochs with an amplitude change exceeding ± 200 μV at any channel were automatically rejected. ERPs were averaged separately for the standard and deviant tones. Amplitudes were scored at Pz and Fz as the maximum positive value in a window of 200 and 1000 ms post-stimulus for both the standard and deviant tones. Peak latency was also scored using the same time window.

Procedure

Information on the brain injury and other characteristics of the patient was gathered from the moment of admission at the intensive care unit in the hospital up to the instance of discharge from the rehabilitation centre. When a patient was registered to EINP the information about the injury as acquired by means of a questionnaire that was filled in by a physician or an assistant.

Two days after a patient had started with EINP, the first measurement of study 1 took place. Measurements were repeated every fourteen days. Dependent on their condition, patients were examined either sitting in upright position in a bed, or sitting in a wheel chair in a quiet room with a constant temperature (23±1 °C). Measurements were always recorded at the same time of the day (from 3:00 to 4:00 p.m.), immediately after the afternoon resting period.

During each measurement a neuropsychologist administered the WNSSP (see Appendix C at the end of this chapter). In addition, the neuropsychologist scored the patient's behaviour according to the observation scales LoC, DRS, and WNSSP. This assessment was performed every two weeks by the same neuropsychologist until the patient was no longer qualified for the rehabilitation programme.

For the patients that participated in the second study, the first measurement was done nine days after a patient admission to the EINP. As in the first study, the measurements were repeated every fourteen days. The patients were always examined while they were lying in a bed in a quiet room with a constant temperature (between 10:30 a.m. and 11:30 a.m., immediately after the morning resting period). In the same week the rehabilitation physician determined the LoC.

The studies were performed until the patient was discharged. Discharge could be the result of various decisions: a) a patient was qualified for regular rehabilitation because of recovery of consciousness and cognitive abilities; b) a patient did not show any recovery during the programme (within a period of at least six weeks), and therefore was indicated for a nursing home; c) a patient deceased. Sometimes patients could not participate in a measurement because of their medical condition.

Long-term outcome was determined by the DRS and GOSE scores at least 2 years after the injury (M = 2.6, SD = 0.28, see Appendix 7, table 1 for the exact time intervals: Toutcome). A rehabilitation physician performed the interviews by telephone with a close relative of the patients (partner or parent).

The norm group was measured once, in the same position and location, at different times of the day. They underwent the same protocol as the patients.

Statistical Analyses

The present longitudinal research was concerned with analyses of change. An observation scale was used that described eight levels of consciousness. On this scale, a score of 1 indicated a comatose state, the scores of 2, 3, and 4 indicated sublevels of the vegetative state, the scores 5, 6, 7 indicated sublevels of the minimally conscious state, and a score of 8 indicated 'full' consciousness (Appendix 3 describes the scale in detail). This observational scale was of ordinal level. The values on the scale express an order from no conscious at all (1=coma) to full consciousness (8). In between the 'levels of consciousness' 1 and 8, the scale describes levels of increasing consciousness through the vegetative and minimally conscious state; however, the values do not indicate the exact magnitude of difference between the categories (e.g., as an interval or ratio level would).

Ordinal data like these are often analysed as if they were continuous data at interval level, that is, by means of methods that imply linear relationships and normally distributed errors. However, the observational data obtained in the present studies are essentially categorical and measured at an ordinal, not an interval level. A better way to deal with such ordinal response variables is to treat them as categorical variables from a multinomial distribution; the ordinal nature of the categories is then taken into account by imposing particular constraints on the odds of responding, i.e., of choosing one category rather than another. Such models are best analysed by means of mixed model analyses, in which the individual change over time is modelled as a random factor (Vermunt & Hagenaars, 2004).

However, such mixed models of categorical data are a relatively new statistical development, and at the time of this project we did not have the necessary tools available to perform this analysis adequately. Therefore, we continued to treat the data as being of interval level, but still modelled the data with a random effect for the change over time. It is acknowledged that this method of analysis is sub-optimal, and that the reliability and validity of the conclusions should be interpreted with care. However, despite this imperfection, the fact that random effects were used to model individual change over time should yield an important advantage over more traditional fixed-effects models (standard univariate or multivariate analyses of variance). In addition, using random effects to model individual change over time also had the advantage that occasionally missing a measurement for a particular patient did not result in that patient being excluded from the entire analysis.

The statistical procedure with random and fixed effects, which was used to analyse the longitudinal data measured in the present thesis, is reminiscent of the analysis of individual growth suggested by Francis et al. (1991), in which growth curves are estimated for individual subjects, and the parameters of these curves are then statistically analysed.

Appendix A

General research Protocol

When	What	Who
At application (even if a waiting list exists, and when it is not yet certain if the patient will be admitted to EINP)	Inform about the research project Requiring applicant and patient information Pass information directly on to research unit	Rehabilitation Physician(s)
When patient information is received by research unit	Application and maintaining of an agenda Announcing the request on research participation to parents and applicants Sending information on the research project and the request on participation to the family of the patient Sending information on the project and procedures and the request to collect patient information to the applicant	Research unit Research unit Research unit Research unit
After admission	Day three after admission: ***study 1,*** day nine after admission: ***study 2**** Requiring ***initial CT-scans*** and ***letter of discharge.*** ***Evaluation of CT-scan by a 'blind' observer***	Research unit Research unit External neurologist
During EINP	Every two (odd) weeks (A): ***study 1*** Every two (even) weeks (B) ***study 2**** Every two weeks observation scales	Research unit
End of EINP	Determination of LoC at discharge ($LoC_{discharge}$)	Rehabilation Physician(s)
Long term outcome	Two years after the injury: interviews on functional outcome by telephone	Rehabilation Physician(s)

Appendix B

Protocols of study 1 (week A) and study 2 (week B)

Week A:	**Autonomic Nervous System** (Heart Rate and Skin Conductance)	
WNSSP	3:00 – 4:00 PM	3 minutes rest – WNSSP – 3 minutes rest

Week B

EEG Tasks: 10:30 – 11:30 AM

Task	**Time (min)**	**Stimuli characteristics**
Rest EEG	3	-
Repetition Priming Paradigm*	10	
Pause	3	-
MMN	12	1500 tones of 70 dB (85% 1000 Hz and 15% 1500 Hz) 500 ms interstimulusinterval
Pause	3	
Passive P300 (oddball)	6	375 tones of 70 dB (80% 1000Hz and 20% 2000Hz) 1000-2000 ms interstimulusinterval (at ramdon)
Active P300 (oddball)	6	375 tones of 70 dB (80% 1000Hz and 20% 2000Hz) 1000-2000 ms interstimulusinterval (at ramdon)
Pause	10	
BAEPs	10	2000 clicks of 70 dB and 10μsec duration, 11 clicks/second (both ears, lefts ear, right ear)
Pause	3	
VEPs	5	300 flash lights, 10μsec duration, 1 flash/second
Pause	3	
SSEPs	11	2000 electrical stimuli, 10 μsec duration, 1 pulse/second (left median nerve, right median nerve)
Rest EEG	3	

*To be published elsewhere

Appendix C

Stimulation protocol according to the WNSSP: Mean duration and standard deviation of the rest and the stimulation periods for the total patient group

	Stimuli	Mean Duration (SD)
Rest period	None	181.4 (14.3)
Auditory stimulation		257.1 (114.5)
	Sound (bell)	
	Verbal commands - shake my hand - open/close mouth - stick out tongue - open/close eyes - raise eyebrows - move (body part)	
Visual stimulation		319.1 (121.5)
	Mirror following (horizontal and vertical tracking)	
	Picture following (horizontal and vertical tracking)	
	Person following (horizontal tracking)	
	Visual commands - shake my hand - open/close mouth - stick out tongue - open/close eyes - raise eyebrows - move (body part)	
Tactile stimulation		143.3 (80.1)
	Touching body	
	Touching mouth with eartip	
	Object Manipulation - Spoon - Comb - Pencil	
Olfactory stimulation	Four different odours	188.3 (47.6)
Rest period	None	180.8 (5.6)

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Chapter 3

Evoked potentials in children and young adults in avegetative or minimally conscious state

Abstract

Objective: Evoked Potentials (EPs) are often used in comatose patients to get insight in their neurological condition. EPs are useful in predicting outcome in comatose patients in the acute phase. In the present study, Brainstem Auditory, Somatosensory and Visual Evoked Potentials (BAEPs, SSEPs and VEPs) were examined in the post-acute phase.

Methods: Twelve vegetative patients were repeatedly examined every two weeks for an average period of 2,6 months. BAEPs, SSEPs and VEPs were related to the patients' recovery from the vegetative state to consciousness, and to a healthy norm group. In addition, the EPs were examined on their prognostic value in the post-acute phase, in predicting recovery to consciousness and long-term functional outcome, by using the prognostic method of Guérit and colleagues (1993).

Results: Neither EP amplitudes nor latencies did significantly change with recovery to consciousness. Only the VEPs significantly differed, when compared to a healthy norm group: amplitudes were smaller, and latencies were longer in the patient group relative to the controls. In addition, only VEPs were able to predict long-term outcome. P2 latency of the VEP predicted outcome two years after the end of the treatment. The N3 component of the VEP predicted both the level of consciousness at the end of the treatment, and long-term functional outcome.

Conclusions: No longitudinal changes were found. It appears that elementary sensory processing in this patient group in the post-acute phase was fully functional. Only elementary visual processing was poorer in patients relative to the controls. The large predictive value of EPs in the acute phase could not exactly be replicated to the post-acute phase. Only VEPs seemed capable of predicting long-term outcome of these patients.

Significance: This is the first study in which VEPs were found to be of predictive value in the post-acute phase. Our results warrants future research on VEPs in vegetative patients.

Introduction

Severe brain injury results in high morbidity and mortality rates. The majority of patients experience long-term or lifelong disabilities, bringing along major costs for family and society. So far there has been limited research concerning the group of young adults, who have the highest risks (Finfer and Cohen, 2001; Jennett, 1996). Many individuals who sustain severe acquired brain injury experience prolonged or permanent disorders of consciousness. Acute severe brain injury inevitably results in coma, a state of loss of consciousness with the eyes closed, with no sleep-wake cycle (Multi-Society Task Force on Persistent Vegetative State, 1994a). If not resulting in death within a period of four to six weeks, this coma will develop into a vegetative state (VS; Jennett and Plum, 1972), where the patient seems awake but not aware: uncommunicative and unresponsive to the environment. If recovery continues, patients regain minimal responsiveness to external stimuli (minimally conscious state, MCS; Giacino et al., 2002), that eventually may result in full recovery of consciousness and responsiveness. Otherwise, patients may remain in a vegetative or minimally conscious state for a long time, or even for the rest of their life.

It is estimated that one to fourteen percent of the traumatic, and twelve percent of the non-traumatic prolonged comatose patients shift into the VS (Multi-Society Task Force on Persistent Vegetative State, 1994a; Multi-Society Task Force on Persistent Vegetative State, 1994b). Fifty two percent of the traumatic and fifteen percent of the non-traumatic vegetative patients do recover to consciousness (Multi-Society Task Force on Persistent Vegetative State, 1994b). Whereas recovery from the VS to consciousness is possible, longitudinal research in the post-acute phase within this group is of great importance. Within this group the question revives whether a patient is going to recover from this state.

The diagnosis of the vegetative and the minimally conscious state is based mostly on clinical observation of behavioural criteria. This method of diagnosis contains several uncertainties. First, observational methods depend on the subjective interpretation of behavioural responses, whereas conscious experience often occurs without behavioural signs. Second, no initial behavioural differences exist between the patients who may recover to consciousness and those who remain permanently vegetative. To obtain complementary objective information about the level of consciousness in non-responsive patients, the present study focused on neurophysiological responses during the recovery from the vegetative state to consciousness. A longitudinal study was performed in which evoked potentials to auditory, visual, and somatosensory stimulation were examined.

Evoked potentials (EPs) are fragments of the electroencephalogram (EEG) that are time locked to a specific environmental stimulus. They can be obtained through each of our senses, and their characteristics depend on the specific features of the specific stimuli. EPs are often used in comatose patients to improve the knowledge on their neurological conditions. Many

studies have demonstrated the usefulness of EPs in predicting mortality and outcome in comatose patients (Amantini et al., 2005; Fischer et al., 2004; Guérit et al., 1993; Mazzini et al., 1999; Wang et al., 2004). A bad outcome is likely to follow when brainstem auditory and somatosensory evoked potentials (BAEPs and SSEPs) fail to appear in the acute phase after severe brain damage (Wang et al., 2004). Especially SSEPs measured in the first week post-injury appear to be most useful to predict a poor outcome (Zandbergen et al., 1998). In addition, when comatose patients were followed longitudinally, the changes in their overall condition were related to the presence, abnormality or absence of BAEPs, SSEPs, and Visual Evoked Potentials (VEPs; Greenberg et al., 1977; Guérit, 2000; Guérit et al., 1993; Rappaport et al., 1981).

The above findings all refer to the acute phase; up to about four to six weeks after the injury. The present study attempts to gain insight into the appearance of BAEPs, SSEPs, and VEPs during the post-acute phase; that is, related to the recovery from the vegetative state to consciousness. It was expected that changes in the amplitude and/or latency of the EPs would concur with recovery. Thus, we expected that the results for the acute phase could be generalised to the post-acute phase. With recovery to consciousness, the EPs in the patients were expected to become increasingly similar to the EPs recorded in a healthy norm group.

Secondly, we examined whether the EPs are of prognostic value in the post-acute phase according to the prognostic method of Guérit and colleagues (1993). This method, which was developed for the acute phase, uses evoked potentials in the auditory, somatosensory, and visual modalities, and is therefore called the 'three-modality evoked potentials' (TMEPs). In this diagnostic and prognostic tool two indices are defined: the 'Index of Brainstem Conduction' (IBSC), obtained from BAEPs and SSEPs, and the 'Index of Global Cortical Functioning' (IGCF), obtained from VEPs and cortical SSEPs. For the IBSC the EPs are first quantitatively evaluated in terms of an auditory or a somatosensory brainstem conduction time. If they are normal, they are also qualitatively evaluated in terms of medullar, pontine or mesencephalic involvement. The IGCF is graded from 0 (normal IGCF) to 5. Grades 1 to 4 refer to increasing degrees of cortical dysfunction: grades 1 and 2 correspond to a variable involvement of the cortical associative areas, and grade 3 corresponds to the sole preservation of primary cortical activities. Grade 4 includes a disappearance of subcortical waves and has uniformly been associated with death or persistent vegetative state (Guérit et al, 1993).

The virtue of the methods proposed by Guérit et al. (1993) is that a number of complex measures are reduced to a single index of cortical functioning, which can be used for diagnosis and prognosis of outcome. The extensive, longitudinal study of Guérit et al. (1993) suggested that two different TMEP models should be used for traumatic and anoxic groups. In addition, they also showed that flash VEPs, which are rarely used, appeared to be of significant additional value. Finally, follow-up measurements revealed improving changes in EP responses, especially in the anoxic cases, which suggests that acute functional brain damage may be reversible.

The TMEP prognostic model in anoxic cases was mainly based on the IGCF. Mild IGCF alterations observed in the first 10 days were associated with a favourable outcome. Strong IGCF alterations observed after the first 24 hours were associated with a poor outcome. In traumatic comas, both IGCF and IBSC were specifically altered. The abnormalities were clustered into four global patterns. Pattern 1 was similar to that observed in anoxic comas: IGCF alterations without evidence of brain-stem dysfunction. Pattern 2 was uniformly characterized by primary midbrain and/or pontine dysfunction, which were found in 40% of the TBI cases. Pattern 3 was interpreted as a pontine lesion caused by transtentorial herniation. Pattern 4 was that of brain death. In the present study, we shall refer to these four patterns as the 'global score', which we attempted to generalise to the post-acute phase as well.

Methods

Participants

Twelve patients with severe brain injury took part in the study between November 2002 and January 2004. Nine patients (75%) were male. Age at the time of injury ranged from 6 to 25 years (M = 16.6 years; SD = 5.3). Time since injury at admission ranged from 1.9 to 6.6 months (M = 3.5 months; SD = 1.5). All but two patients suffered from TBI caused by traffic accidents. All patients participated in this study following informed consent given by one of the parents, a legal representation or partner. The duration of the patients' participation in the programme ranged from 1.5 to 4.3 weeks (M = 2.6 months weeks; SD = 0.8). For the sake of comparison with other papers, these patients are not numbered 1 to 12, but 17 to 28 (Appendix 7).

A norm group consisting of 22 persons (12 male, 55%), matched for mean age ($t(32)$ = 0.67, p = 0.51), was investigated on a single occasion. All of the participants took part in this study following informed consent given by one of the parents or a legal representation (age < 16 years), or by themselves (age ≥ 16). The BAEPs and the SSEPs could not be recorded reliably in the whole group, due to movement artifacts and environmental noise. The BAEPs could be successfully recorded in 16 persons (9 male, 56%, mean age 18.5 years, $t(23)$ = 1.05, p = 0.31), and the SSEPs in 15 persons (7 male, 47%, mean age = 18.8 years, $t(25)$ = 1.21, p = 0.24).

The study has been approved by METTOP (a Dutch Medical Ethics Committee for research with patients).

Data acquisition and analysis

Electroencephalographical activity (EEG) was recorded using actively shielded pin-electrodes (ActiveTwo System, BioSemi, The Netherlands; sampling rate 8kHz; Common Mode Rejection Ratio > 80 dB). The total equipment was approved on safety by a Metron QA-90

Safety tester in the Tweesteden Hospital (Tilburg, The Netherlands). The electrodes were placed using a head cap and electrode gel (Parker Signa) according to the 10/20 system, at F3, Fz, F4, C3, Cz, C4, Pz, and Oz, referenced to algebraically linked mastoids. Horizontal EOG was recorded from two electrodes placed at the outer canthi of both eyes. Vertical EOG was recorded from infraorbital and supraorbital regions of the two eyes in line with the pupil.

Each EP consists of a number of distinct components. The relation of these components to the underlying brain structures is summarised in Table 1. The IBSC, IGHF, and the global score were calculated based on the different EP components (see the Appendix at the end of this chapter for details). In case of asymmetry of the SSEPs (difference between left and right median nerve SSEPs), the best side was chosen to estimate the IGHF. Both of the indices were determined for each measurement based on visual inspection of the components.

Table 1. The relation between EP components and brain structures

	I	**II**		**III**		**IV**	**V**	
BAEPs	cranial nerve	cochlear nucleus and cranial nerve		(ipsilateral) superior olivary nucleus		lateral lemniscus	inferior colliculus	
	P14	**N20**	**P20**	**P25 (22)**	**P27**	**N30**	**P45**	**N60**
SSEPs	medial lemniscus	primary somatosensory cortex (parietal)	primary motor cortex (frontal)	vertex (central)	primary sensory cortex (parietal)	primary motor cortex (frontal)	rolandic fissure peri-rolandic region (pre- and postcentral gyri) (central)	secondary somatosensory cortex (SII) parieto-rolandic operculum fronto-central
Flash VEPs	**P1**	**N2/III**	**P2**	**N3/VII**				
	optic nerve	optic chiasm	Vertex (central)	peristriate and striate occipital cortex				

Brainstem Auditory Evoked Potentials (BAEPs)

The auditory stimuli were 2000 clicks, with an intensity of 70 dB SPL, duration of 10 μsec, and a frequency of 11 Hz. The tones were delivered both binaurally and unilaterally through insert earphones in three sessions. EEG signals were band-pass filtered (100 – 3000 Hz, 48 dB/octave). The raw data were segmented into 2000 epochs, including a 5 ms prestimulus baseline, and a 10 ms poststimulus response time. BAEPs were examined at the Cz electrode. Different references were calculated off-line. Bilateral measurements were analysed both with left and right mastoids as a reference (M1 or M2). For the unilateral sound presentations the mastoid contralateral to the stimulated ear was used. Thus, the BAEPs to clicks presented to the right ear were recorded from Cz with a left mastoid reference (M1), and

the BAEPs following clicks to the left ear were recorded from Cz versus the right mastoid (M2). Only the unilateral measurements are presented here, because they showed the different peaks most clearly (Nuwer et al., 1994).

The BAEP exists of five negative peaks (I – V) each corresponding to activity in a specific part of the auditory pathway (Table 1). Peak I, III and V were examined on their presence and their interpeak latencies. All peaks were scored visually on individual subject's averages by one and the same experienced researcher.

Somatosensory Evoked Potentials (SSEPs)

The somatosensory stimuli were 2000 electrical pulses, with an intensity of maximal 20 mA, duration of 10 μsec, and a frequency of 3 Hz. The stimuli were delivered unilaterally to the median nerve of the left and right wrist in two sessions. EEG signals were band-pass filtered (3 - 200 Hz, 48 dB/octave). EOG artefacts were corrected according to a linear regression procedure (Gratton et al., 1983).

The raw data were segmented into 2000 epochs, 10 ms to 100 ms poststimulus response time to avoid the large stimulus artefacts. Dependent of the stimulated wrist, and the components of interest, SSEPs were examined at Pz, C3, C4, Fz, F3, and F4. The mastoid ipsilateral to the stimulated wrist was used as reference.

The SSEP exists of short- and long-latency components (Table 1). The long-latency components are referred to as cortical SSEPs (cSSEPs). The presence of each component was scored, and if present, their amplitude and latency.

Visual Evoked Potentials (VEPs)

The visual stimuli were 300 white flashlights presented with a frequency of 1 Hz. The flashlights were presented bilateral using a 'White Flash Nihon Kohden model EEG-4314 F/G'. The lamp was in distance of about 30cm of the participant. EEG signals were band-pass filtered (3 – 100 Hz, 48 dB/octave). EOG artefacts were corrected according to a linear regression procedure (Gratton et al., 1983).

The raw data were segmented into 300 epochs, including a 5 ms prestimulus baseline, and a 500 ms poststimulus response time. Peaks amplitudes and latencies were examined at the Oz electrode with reference to Fz.

The VEPs exists of alternating negative and positive waves. Odom et al. (2004) denoted these waves as N1, P1, N2, P2, N3, P3, respectively. Sometimes the nomenclature of (Cigánek, 1961) is used, in which the peaks are labelled sequentially by Roman numerals. The long-latency peaks N2 (III), P2, and N3 (VII) were examined on their presence, their interpeak latency, and their peak-to-peak amplitudes: N2 – P2 and P2 – N3.

Observation Scales

To assess the Level of Consciousness (LoC) a categorisation was used based on the definitions described by the 'International Working Party Report on the Vegetative State' (Andrews, 1996) and the Aspen Neurobehavioural Conference (Giacino et al., 1997). The categorisation system describes a comatose state, three vegetative sub-states, three non-vegetative sub-states, and a conscious state (see Appendix 2 for the classification scheme in detail).

This classification scale showed high reliability and validity (Eilander et al., 2005). The inter- rater reliability (Spearman's rho) varies between 0.85 and 0.94. The inter-rater agreement (Cohen's weighted Kappa) varies between 0.90 and 0.95. The intra-rater reliability is 0.96 and the intra-rater agreement is 0.94. Correlation of the scores of the rated scores with the Western Neuro Sensory Stimulation Profile (WNSSP, Ansell et al., 1989) varies between 0.85 and 0.90, and with the Disability Rating Scale (DRS) (Rappaport et al., 1982) between 0.88 and 0.94 (Eilander et al., submitted).

Overall LoC at the end of the programme ($LoC_{discharge}$) was determined by the rehabilitation physician, based on Appendix 3, after a discussion with the multidisciplinary treatment team about each patient.

To determine the long-term functional outcome, the DRS (Rappaport et al., 1982) as well as the GOSE (Wilson et al., 1998) were administered. The DRS consists of eight items, which can be summed up to values from 0 to 29. A high score on an item indicates a low level of functioning on that aspect. To make the two scales more comparable, the DRS was reduced to 8 categories according to Rappaport et al. (1982): 1=dead (score 30), 2=vegetative state (score 22-29), 3=extremely severe disabled (score 17-21), 4=severely disabled (score 12-16), 5=moderately severe disabled (score 7-11), 6=moderately disabled (score 4-6), 7=mildly to partially disabled (score 1-3), and 8=no disability (score 0).

The GOSE is a one-item rating scale including eight outcome categories and can be administered through a structured interview (Wilson et al., 1998). Outcome categories are: 1=dead, 2=vegetative state, 3=lower severely disabled, 4=upper severely disabled, 5=lower moderately disabled, 6=upper moderately disabled, 7=lower good recovery, 8=upper good recovery.

Procedure

Nine days after a patient was admitted to the RCL the first measurements took place. Patients were examined while they were lying in a bed in a quiet room with a constant temperature (23 ± 1 °C). All measurements were done every two weeks at the same time of the day; between 10:30 a.m. and 11:30 a.m.. The total measurement of the EPs lasted 25 minutes (BAEPS bilateral, left ear, right ear: 9 min, SSEPs left and right: 10 min, VEPs: 5 min). LoC was determined in the same week as the EP measurements by a rehabilitation physician, based on

a discussion by the multidisciplinary treatment team. These assessments were performed until the patient was discharged. Discharge followed when a) a patient was qualified for regular rehabilitation because of recovery of consciousness and cognitive abilities, or b) a patient did not show any recovery in a period of at least six weeks during the programme.

Long-term outcome was determined by the DRS and GOSE scores at least 2 years after the injury (M=2.6, SD=0.28, see the table in Appendix 7 for the exact time intervals). A rehabilitation physician performed the interviews by telephone with a close relative of the patients (partner or parent).

The norm group was measured once, in the same position and location, at different times of the day. They performed on exactly the same tasks as the patients.

Statistical analysis

The longitudinal changes of EP amplitude and latency were analyzed as a function of LoC using a linear Mixed Model procedure. This procedure is especially adequate to analyze changes in heterogeneous groups such as patients recovering from brain injury (Francis et al., 1991). Mixed models use all available data, can properly account for correlation between repeated measurements on the same subject, have greater flexibility to model time effects (Keselman et al., 2001). LoC and the individual subjects were included as random factors.

One-sided independent samples t-tests were used to examine group effects for the patients in the different LoCs versus the healthy control group. The predictive values of the EPs were examined by ROC analyses and linear regression analyses.

Results

Outcome

Table 2 presents an overview of all the patients who were part of the present study. It shows that the patients' Level of Consciousness at the time of the first measurement was 3.75 on average (vegetative – reflexive state), and they progressed to an average level of 6 (minimally conscious state – inconsistent reactions) when they were discharged from the programme. We attempted to predict the LoC at discharge from the initial LoC by a regression analysis. This analysis did not result in a significant model, however (β = 0,20, t = 0.62, p = 0.55). Thus, final outcome could not be predicted from the initial consciousness scores.

Table 2 also shows the long-term outcome scores. On average, the patients exhibited a score of 4.4 on the DRS (moderately severe disability), and 3.1 on the GOSE (lower severe disability).

Evoked Potentials

The different components of the EPs could not always be scored reliably. Recordings were sometimes plagued by excessive noise, movements, or general resistance on the part of the patients. Table 2 lists, separately for each component, the number of successfully realised measurements. It can be seen from the table that nearly all measurements of the BAEPs and the VEPs were successful. However, the SSEPs could often not be interpreted; therefore only their presence was scored, which was used to calculate the IBSC, IGCF, and global score of Guérit et al.'s (1993) classification method, which are also listed in Table 2. Representative examples of the EPs are presented in Figure 1.

Longitudinal changes in EPs

The latencies of the different BEAP peaks were determined in each measurement, and then collapsed into the different LoCs. The resulting latencies and inter peak latencies for the unilateral BAEPs are listed in Tables 3 and 4, for clicks presented to the right and left, respectively. Statistical analysis (Table 5) revealed that none of the BAEP peak latencies or inter peak latencies varied as a function of the LoC. Only the inter peak latency I-V of the BAEPs to clicks presented to the left ear tended to vary as a function of the LoC, but otherwise no statistically significant changes as a function of the LoC were found in the BAEPs. Thus, BAEPs latencies did not seem to change with recovery to consciousness.

Table 2. Patients' details (further information on these patients can be obtained in Appendix 7), along with an overview of the recorded EPs, and the outcome scales

Ptn	TM	F/M	Age	Cause	BAEPs	SSEPs	cSSEPs	VEPs	IBSC	IGCF	Global score	LoC initial	LoC discharge	DRS	GOSE
17	6,6	M	17,6	traffic accident	5/5	3/3	3/3	3/4	0	1-3	3	4	4	3	3
18	3,6	M	6,0	near drowning		2/2	2/2	2/2	0	1	1	5	8		
19	3,1	M	20,8	traffic accident	6/6	2/6	1/6	5/5	mesencephalic	1	2	4	4	4	3
20	6,1	M	15,4	traffic accident	6/6	3/5	3/5	6/6	mesencephalic	1-2	2	3	5	4	3
21	2,4	M	25,2	traffic accident	4/4	5/5	5/5	4/5	0	1	1	4	8	6	3
22	2,9	M	8,4	cerebral haemorrhages	5/5	5/5	5/5	4/4	0	1-2	1	4	7	7	3
23	1,9	F	18,8	traffic accident	7/7	4/13	4/13	8/8	0	1	1	3	8	4	3
24	4,5	M	17,5	traffic accident	1/1	1/2	1/2	2/2	0	1	1	4	8	7	6
25	2,6	M	21,8	traffic accident	7/7	6/10	4/10	6/6	mesencephalic	1-2	2	4	4	3	3
26	2,2	F	15,7	traffic accident	4/4	6/8	5/8	3/3	0	1-2	2	4	8	5	3
27	2,9	M	17,2	traffic accident	10/10	8/17	6/17	9/10	mesencephalic	1-3	2	3	5	1	1
28	3,6	F	15,2	pneumonia + sepsis shock	4/4	6/9	6/9	1/4	mesencephalic	2-3	3	3	3		

Ptn = patient; TM: time between injury and first measurement in months; F = Female; M = Male; Age = Age at time of injury; cSSEPs = cortical Somatosensory Evoked Potentials; BAEPs, SSEPs, cSEPs, and VEPs: number of components identified out of total number of measurements; IBSC = index of brain-stem conduction; IGCF = Index of global cortical functioning; LoC initial= Level of consciousness at first measurement; LoCdischarge = Level of Consciousness at the end of EINP; DRS = Disability Rating Scale; GOSE = Glasgow Outcome Scale extended

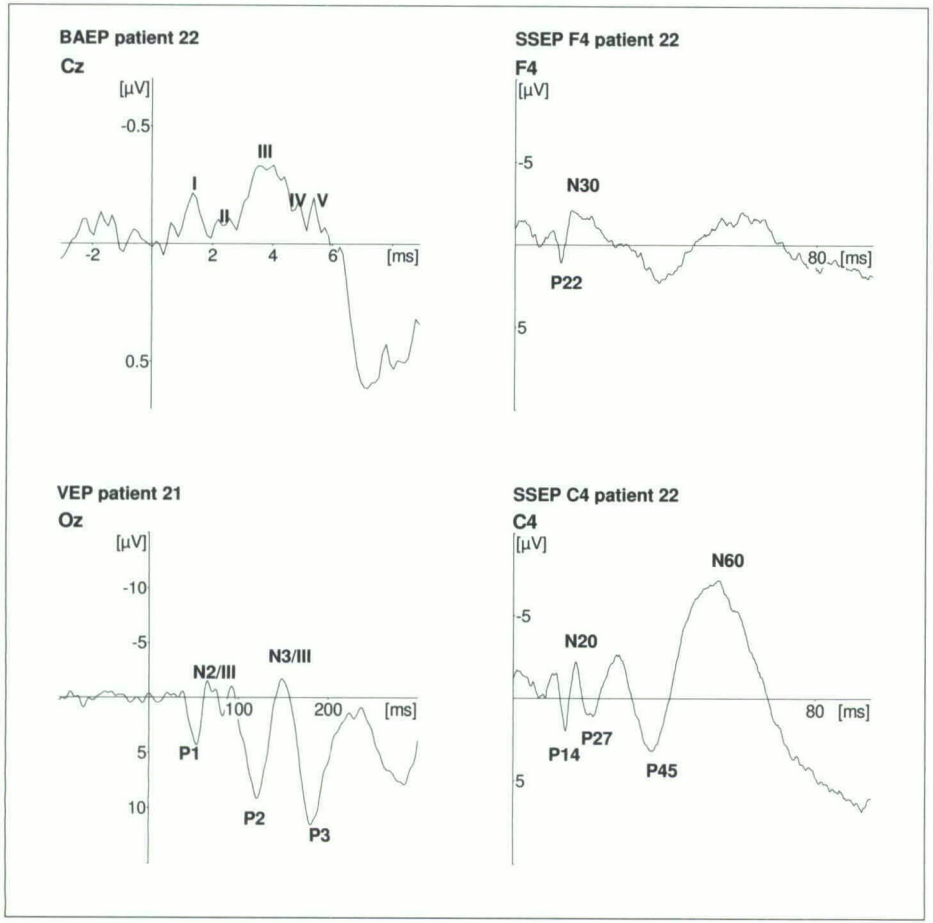

Figure 1

Representative examples of Evoked Potentials in the patient group:

BAEP patient 22

Brainstem Auditory Evoked Potential after right ear stimulation of patient 22 (Cz-M1): wave I, II, III, IV

VEP patient 21

Visual Evoked Potential after binocular stimulation of patient 21 (Oz-Cz): P1, N2/III, P2, N3/III, P3

SSEP F4 patient 22

Somatosensory Evoked Potential after right median nerve stimulation of patient 22 (F4-M1): P22,N30

SSEP C4 patient 22

Somatosensory Evoked Potential after right median nerve stimulation of patient 22 (C4-M1): P14, N20, P27, P45, N60

Table 3. BAEPs right ear: Wave I, II, III, IV, V, and inter peak Latencies I-II, III-V, I-V, in milliseconds (standard deviations in parentheses), by Level of Consciousness (LoC). The number of measurements for each LoC is also listed (N).

		BAEPs Mean (Standard Deviation)							
		Latencies (milliseconds)					Interpeak latencies (milliseconds)		
LoC	N	I	II	III	IV	V	I-III	III-V	I-V
Norm	16	1.65 (.60)	2.78 (.60)	3.78 (.45)	4.84 (.39)	5,47 (.25)	2.15 (.52)	1.69 (.32)	3.82 (.44)
2	2	1.83 (.06)	2.81 (.86)	3.78 (.35)	4.53 (.05)	5.83 (.04)	1.95 (.35)	2.08 (.35)	4.02 (.31)
3	9	1.40 (.28)	2.60 (.53)	3.82 (.40)	4.87 (.53)	5.52 (.62)	2.43 (.52)	1.70 (.59)	4.12 (.74)
4	9	1.26 (.32)	2.88 (.45)	4.01 (.37)	4.79 (.61)	5.43 (.54)	2.75 (.50)	1.41 (.47)	4.16 (.54)
5	9	1.41 (.35)	2.88 (.67)	3.95 (.44)	4.96 (.64)	5.65 (.49)	2.54 (.68)	1.70 (.64)	4.23 (.46)
6	2	1.83 (.25)	2.56 (.35)	4.03 (.35)	4.76 (.17)	5.37 (.17)	2.20 (.35)	1.34 (.52)	3.54 (.17)
7	2	1.40 (.60)	2.75 (.09)	3.72 (.26)	4.70 (.26)	5.25 (.35)	2.32 (.86)	1.53 (.09)	3.85 (.95)

Table 4. BAEPs left ear: I, II, III, IV, V, and inter peak Latencies I-II, III-V, I-V, in milliseconds (standard deviations in parentheses), by Level of Consciousness (LoC). The number of measurements for each LoC is also listed (N).

		BAEPs Mean (Standard Deviation)							
		Latencies (milliseconds)					Interpeak Latencies (milliseconds)		
LoC	N	I	II	III	IV	V	I-III	III-V	I-V
Norm	22	1.47 (.37)	2.74 (.61)	3,93 (.57)	4,80 (.51)	5,60 (.26)	2.47 (.56)	1.67 (.41)	4.13 (.51)
2	1	1.83	2.56	3.91	4.52	5.01	2.08	1.10	3.17
3	8	1.40 (.34)	2.36 (.51)	3.59 (.54)	4.53 (.08)	5.40 (.31)	2.18 (.74)	1.74 (.51)	3.99 (.52)
4	8	1.45 (.34)	2.76 (.57)	3.81 (.32)	4.58 (.16)	5.36 (.29)	2.36 (.59)	1.54 (.34)	3.91 (.44)
5	11	1.39 (.35)	2.92 (.42)	3.87 (.49)	4.69 (.23)	5.74 (.62)	2.49 (.59)	1.86 (.62)	4.35 (.50)
6	3	1.14 (.35)	2.48 (.55)	4.03 (.44)	4.60 (.14)	5.17 (.39)	2.89 (.14)	1.14 (.25)	4.03 (.32)
7	2	1.04 (.09)	1.95 (.05)	3.91 (.69)	4.33 (.26)	5.98 (.52)	2.87 (.78)	2.08 (1.21)	4.94 (.43)

Table 5. Statistical tests on BAEP peak latencies, as a function of Level of Consciousness (mixed model)

	BAEPs F-value (p-value)					
Wave	Right Ear			Left Ear		
	F	*df*	*p*	*F*	*df*	*p*
I	1.72	5;8.4	.15	1.14	5;27.0	.37
II	0.41	5;13.6	.84	2.07	5;26.0	.10
III	0.40	5;27.0	.85	0.45	5;9.53	.81
IV	0.43	5;17.4	.82	1.94	5;14.86	.15
V	0.49	5;15.9	.78	1.82	5;27.0	.14
I-III	0.91	5;27.0	.49	0.81	5;8.48	.58
III-V	0. 81	6;23.9	.58	0.72	5;11.13	.62
I-V	1.05	6;27.3	.42	***2.91***	***5;27.0***	***.03****

****p < 0.05***

The amplitudes and latencies of the different VEP components are presented in Table 6, separately for each LoC. Again, none of VEP peak amplitudes or latencies varied as a function of the level of consciousness. Table 7 shows the results of the mixed model tests, which does not list any statistically significant effect of LoC, neither on VEP amplitudes nor on latencies. Just as for the BAEP components, none of the VEP components appear to change with recovery to consciousness.

Table 6. Amplitudes (μV) and latencies (ms) of the flash VEPs recorded at Oz versus Cz (standard deviations in parentheses), by Level of Consciousness (LoC). The number of measurements for each LoC is also listed (N).

		VEP amplitudes (μV)			VEP latencies (milliseconds)			Peak to Peak magnitude (μV)	
LoC	N	N2	P2	N3	N2	P2	N3	N2-P2	P2-N3
Norm	22	-2.38 (4.23)	12.84 (6.36)	-8.17 (6.81)	62.82 (15.36)	109.24 (12.39)	163.31 (9.32)	16.52 (7.75)	21.31 (10.75)
2	2	-1.24 (1.86)	-0.48 (8.02)	-2.77 (1.67)	144.35 (34.96)	138.92 (22.96)	251.83 (31.76)	6.99 (1.07)	8.45 (2.34)
3	11	-3.11 (2.89)	4.06 (4.16)	-1.38 (2.74)	126.40 (44.34)	208.93 (66.35)	262.04 (40.45)	7.76 (5.27)	6.39 (5.45)
4	20	-2.93 (2.80)	5.50 (4.39)	-2.37 (2.75)	132.83 (44.81)	195.47 (42.03)	277.98 (53.61)	8.80 (5.34)	8.20 (6.25)
5	11	-2.98 (2.63)	3.58 (4.11)	-2.37 (1.48)	134.51 (32.81)	176.66 (32.94)	253.86 (48.31)	8.33 (3.58)	7.24 (3.21)
6	3	-2.39 (5.09)	4.42 (5.68)	0.79 (0.44)	96.96 (69.43)	148.48 (24.73)	261.35 (23.21)	10.52 (4.45)	6.61 (3.36)
7	4	-1.79 (4.09)	5.56 (2.00)	-1.80 (2.33)	124.42 (63.02)	183.81 (69.25)	258.79 (56.08)	9.05 (.76)	8.02 (1.42)
8	1	-2.76	8.59	-3.27	150.51	184.57	234.01	11.35	11.86

Table 7. Statistical tests on VEP amplitudes and latencies, by Level of Consciousness (mixed model)

	VEPs F-value (p-value)					
Peak	Amplitudes			Latencies		
	F	*df*	*p*	*F*	*df*	*p*
N2	0.27	6;40.74	.95	0.58	6;43.76	.75
P2	0.82	6;40.35	.56	0.74	6;41.65	.62
N3	0.77	6;43.76	.60	0.53	6;42.66	.78
N2-P2	0.36	6;42.42	.90			
P2-N3	0.59	6;40.06	.74			

As mentioned above, the SSEPs could not be reliably scored on amplitude and latency, but their presence or absence was used to calculate the IBSC, IGCF, and the global score. The results of these summary measures are given in Table 8, separately for each LoC. None of the summary scores varied as a function of LoC (IBSC: $F(5,24.09) = 0.62$, $p = .89$; IGCF: $F(5, 26.64) = 0.30$; $p = .91$; global score: $F(5,27.93) = 1.28$, $p = .26$). It appears that none of the composite summary scores changed with recovery to consciousness.

Table 8. Index of Brainstem Conduction (IBSC), Index of Global Cortical Function (IGCF), and the Global score (Means and Standard Deviation), as a function of LoC

LoC	IBSC	IGCF	Global score
2	0.50 (.70)	2.00 (1.41)	2.00 (1.41)
3	0.67 (.50)	2.17 (.94)	2.00 (0.85)
4	0.75 (.44)	2.25 (.94)	1.63 (0.82)
5	0.53 (.52)	2.07 (1.03)	1.36 (0.63)
6	0.50 (.58)	1.75 (.96)	1.50 (1.00)
7*	0.40 (.55)	1.80 (1.10)	1.00 (0.00)

Taken together, the results of the longitudinal EP analyses suggest that neither any of the EP components, nor any of the composite summary measures, changed with behaviourally observed recovery to consciousness, as determined by the LoC scale. We shall now turn to the question whether any of the EP components recorded in the patients were differed from those recorded in normal, healthy subjects.

Comparison of EPs between patients and healthy controls

The data collapsed into each LoC were statistically tested against the healthy control group by means of t-tests. The results of the statistical tests are presented in Tables 9 and 10, for right and left BAEPs, respectively. Overall, the BAEP latencies for the patients were statistically indistinguishable from the healthy controls, despite sometimes large differences in overall morphology. Together with the finding of no longitudinal trends, presented above, the conclusion seems warranted that the BAEP latencies in the patients were indistinguishable from normal healthy controls. For the sake of completeness, we also tested each LoC against the normal controls (Tables 9 and 10), and some differences were noted, especially in the lower LoCs.

Table 9. Statistical tests of BAEP latencies (right ear), patient group (by LoC and overall) versus normal controls

T-values (df)		Healthy controls versus LoC					
		Overall	2	3	4	5	6
Latencies	I	-1.73 (32)	-1.47 (19)	-0.61 (18)	-0.98 (16)	-0.14 (17)	-0.76 (16)
	II	-0.12 (32)	0.39 (19)	0.06 (18)	-0.61 (16)	0.21 (17)	-1.51 (16)
	III	1.11 (31)	0.29 (18)	0.16 (17)	0.21 (15)	1.27 (16)	1.02 (15)
	IV	-0.08 (32)	-0.56 (19)	0.91 (18)	-0.88 (16)	0.89 (17)	-0.5 (16)
	V	0.25 (32)	-0.32 (19)	***1.72 (18)****	-0.82 (16)	1.09 (17)	-0.13 (16)
Interpeak Latencies	I-III	***2.53 (31)*****	***1.76 (18)****	0.77 (17)	1.26 (15)	1.22 (16)	1.69 (15)
	III-V	-0.75 (31)	-0.52 (18)	1.06 (17)	-0.89 (15)	-0.53 (16)	-1.46 (15)
	I-V	1.93 (32)	1.67 (19)	***1.76 (18)****	0.81 (16)	0.90 (17)	0.98 (16)

p < .05. ****p < .01.

Table 10. Statistical tests of BAEP latencies (right ear), patient group (by LoC and overall) versus normal controls

T-values (df)		Healthy controls versus LoC					
		Overall	2	3	4	5	6
Latencies	I	-0.92 (34)	0.08 (16)	0.38 (17)	-1.05 (16)	-0.17 (16)	-1.27 (15)
	II	-1.14 (33)	-1.43 (16)	-0.35 (16)	-0.84 (16)	0.03 (16)	-0.47 (15)
	III	-1.76 (34)	***-3.23 (16)***	-0.30 (17)	***-2.68 (16)***	0.05 (16)	-0.11 (15)
	IV	-1.98 (34)	-0.99 (16)	-0.55 (17)	-1.35 (16)	-0.57 (16)	-0.55 (15)
	V	-0.43 (34)	-0.08 (16)	-1.05 (17)	*-2.05 (16)*	0.89 (16)	-1.24 (15)
Interpeak Latencies	I-III	-0.93 (34)	***-2.47 (16)****	-0.45 (17)	-1.18 (16)	0.15 (16)	0.79 (15)
	III-V	1.00 (34)	***2.25 (16)****	-0.40 (17)	0.96 (16)	0.66 (16)	0.79 (15)
	I-V	0.26 (34)	-0.10 (16)	0.83 (17)	-0.52 (16)	0.77 (16)	0.26 (15)

p < .05. **p < .01.

An entirely different pattern emerges for the flash VEPs. The relevant statistical tests are presented in Table 11. Overall VEP latencies were longer and amplitudes were smaller in the patients relative to the controls, except for the N2 component. Because longitudinal trends were absent, each indididual LoC is different from the normal controls as well. Taken together, these data indicate that there were marked differences in VEP amplitude and latencies between the patients and the controls, but these differences did not depend on the specific LoC of the patients.

Table 11. Statistical tests of VEP amplitudes and latencies, patient group (by LoC and overall) versus normal controls

T-values (df)		Healthy controls versus LoC						
		Overall	2	3	4	5	6	7
Amplitudes	N2	-0.11 (47)	0.37 (22)	-0.38 (26)	-0.56 (29)	-0.14 (24)	0.45 (22)	0.67 (23)
	P2	***-5.46 (47)******	***-2.80 (22)****	***-2.91 (26)****	***-3.10 (29)****	***-2.80 (24)****	***-2.13 (22)****	***-1.80 (23)****
	N3	***4.53 (47)******	***1.10 (22)***	***2.33 (26)****	***2.34 (29)****	***1.79 (24)****	***1.83 (22)****	***1.72 (23)****
Latencies	N2	***7.46 (47)******	***6.59 (22)******	***5.23 (26)******	***7.01 (29)******	***8.38 (24)******	***3.12 (22)****	***5.29 (23)******
	P2	***8.13 (47)******	***3.08 (22)******	***7.53 (26)******	***10.80 (29)******	***9.44 (24)******	***3.38 (22)****	***5.93 (23)******
	N3	***11.44 (47)******	***5.98 (22) ******	***9.29 (26)******	***9.58 (29)******	***8.22 (24)******	***6.40 (22)******	***6.52 (23)******
Peak to Peak Amplitudes	N2-P2	***-4.63 (47)******	***-1.70 (22)****	***-2.47 (26)****	***-2.57 (29)****	***-2.21 (24)****	-1.28 (22)	-1.66 (23)
	P2-N3	***-5.98 (47)******	-1.66 (22)	***-3.14 (26)****	***-0.30 (29)****	***-2.67 (24)****	***-2.01 (22)****	***-2.07 (23)****

p < .05. **p < .01. ***p < .001

Predictive value of Evoked Potentials

It was noted above that the level of consciousness at discharge of the programme could not be predicted based on the level of consciousness at the start of the program. We now turn to the question whether the LoC at discharge, and the long-term outcome measures, can be predicted by any of the EP measures collected on the first measurement at the start of the programme. The results of the regression analyses used to predict the outcome scales by means of the initial BAEP latencies are presented in Tables 12 and 13 for right and left ear, respectively. It can be seen in the tables that none of the BAEP latencies showed a significant predictive value for outcome.

Table 12. Prediction of outcome scales by right BAEP latencies at the first measurement: Waves I, II, III, IV, V, and inter peak latencies I-III, III-V, I-V.

		Outcome Scales								
		Level of Consciousness at discharge			Long term outcome: Disability Rating Scale			Long term outcome: Glasgow Outcome Scale - Extended		
		B	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
Latencies	I	1.97	1.29	0.53	0.07	1.49	0.02	-0.26	0.59	-0.19
	II	-0.15	0.69	-0.09	0.04	0.73	0.02	0.04	0.30	0.06
	III	0.07	0.54	0.05	-0.24	0.52	-0.20	-0.18	0.20	-0.38
	IV	0.16	0.41	0.16	-0.07	0.41	-0.07	-0.14	0.15	-0.38
	V	0.21	0.36	0.23	-0.00	0.36	-0.00	-0.11	0.14	-0.34
Interpeak Latencies	I-III	-0.33	0.72	-0.18	-0.47	0.70	-0.29	-0.28	0.27	-0.43
	III-V	1.17	0.83	0.50	0.75	0.88	0.35	-0.17	0.38	-0.20
	I-V	0.14	0.45	0.12	-0.01	0.45	-0.01	-0.15	0.17	0.36

Table 13. Prediction of outcome scales by left BAEP latencies at the first measurement: Waves I, II, III, IV, V, and inter peak latencies I-III, III-V, I-V.

		Outcome Scales								
		Level of Consciousness at discharge			Long term outcome: Disability Rating Scale			Long term outcome: Glasgow Outcome Scale - Extended		
		B	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
Latencies	I	4.34	1.95	0.67	0.86	2.99	0.13	-1.27	1.91	-0.28
	II	4.07	1.02	0.85	2.82	1.99	0.54	1.64	1.37	0.47
	III	2.01	1.10	0.60	0.40	1.74	0.10	-0.44	1.14	-0.17
	IV	-2.49	2.32	-0.40	-4.41	1.94	-0.71	-2.44	1.46	-0.60
	V	0.98	1.69	0.23	-1.16	1.86	-0.27	-0.23	1.27	-0.08
Inter peak Latencies	I-III	1.22	1.59	0.30	0.14	1.98	0.03	-0.01	1.31	-0.01
	III-V	-2.57	1.54	-0.56	-2.21	2.01	-0.44	0.40	1.47	0.12
	I-V	-0.65	1.45	-0.18	-1.01	1.51	-0.29	0.19	1.04	0.08

p < .05. **p < .01.

The results of the analyses for predicting outcome by means of initial VEP amplitudes and latencies are presented in Table 14. The table shows that the level of consciousness at discharge of the program could be successfully predicted by the amplitude of the N3 and the size of the P2-N3 complex at the first measurement. More negative (greater) N3 amplitude and a greater P2/N3 complex predicted higher LoC scores at the end of treatment. VEP latencies did not predict LoC at discharge. However, initial VEP latencies were of large prognostic value in predicting *long-term outcome* (DRS and GOSE), not LoC, at the end of treatment.

Table 14. Prediction of outcome scales by VEP amplitudes and latencies at the first measurement.

		Outcome Scales								
		Level of Consciousness at discharge			Long term outcome: Disability Rating Scale			Long term outcome: Glasgow Outcome Scale - Extended		
		B	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
Amplitudes	N2	-0.11	0.24	-0.15	0.32	0.22	0.46	0.18	0.14	0.41
	P2	0.23	0.11	0.58	-0.08	0.12	0.23	0.06	0.08	0.28
	N3	-0.34	0.15	***-0.59****	-0.12	0.19	-0.22	-0.23	0.09	***-0.65****
Latencies	N2	-0.01	0.01	-0.38	-0.02	0.01	***-0.67****	-0.02	0.01	***-0.74****
	P2	-0.01	0.01	-0.23	-0.03	0.01	***-0.86****	-0.02	0.00	***-0.80****
	N3	-0.00	0.01	-0.14	-0,02	0.01	***-0.64****	-0.01	0.00	***-0.64****
Peak to Peak Magnitudes	N2-P2	0.19	0.10	0.56	-0.13	0.10	0.40	0.01	0.07	0.06
	P2-N3	0.16	0.07	***0.63****	-0.10	0.08	-0.06	0.07	0.05	0.45

****p < .05. **p < .01.***

Finally, the prognostic value of the composite measures developed by Guérit et al. (1993) was also investigated. The results of the analyses in which the scores of the summary measures at the beginning of treatment were used to predict final outcome, are listed in Table 15. It appears from the table that the summary scores were of little prognostic value in this group of vegetative patients. Only the initial global score predicted long-term outcome assessed by the DRS.

Table 14. Regression analyses classification Guérit et al. (1993)

Predictive variables Classification Guérit et al. (1993)	Outcome Scales								
	Level of Consciousness at discharge			Long term outcome: Disability Rating Scale			Long term outcome: Glasgow Outcome Scale - Extended		
	B	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
IBSC	-1.13	1.23	-0.28	-1.81	1.23	-0.46	0.14	0.88	0.06
IGCF	-0.50	0.64	-0.24	-0.52	0.68	-0.26	0.33	0.43	0.26
Global Score	-0.93	0.61	0.44	-1.19	0.53	***-0.62****	-0.55	0.38	0.46

****p < .05.***

Discussion

The purpose of the present study was twofold. We attempted to track longitudinal changes in EPs of individual patients when they progressed from the vegetative state to consciousness, and we tried to predict outcome by different EP measures.

The results on the longitudinal changes were clear-cut; no changes occurred as a function of increasing level of consciousness, neither in amplitude nor in latency. The summary measures IBSC, IGCF, and global score, calculated according to the method proposed by Guérit et al. (1993), did not change as a function of the level of consciousness either. The absence of any longitudinal changes could be interpreted as a indication that the elementary sensory processing in this patient group was fully functional. We therefore compared the EP measures of the patients to a healthy control group. The SSEPs could not be reliably scored so that patients could be compared to controls. For the BAEPs, no differences between patients and controls were found, so that the conclusion of intact elementary auditory processing seems warranted. For the VEPs, however, this does not seem to be the case, as the amplitudes were consistently smaller and the latencies consistently longer in the patients relative to the controls. It thus seems that elementary visual processing was poorer in the patients compared to the controls; however, this did not change during the course of the treatment programme.

We attempted to predict final outcome on the basis of early measurements. The level of consciousness at the end of the treatment programme could not be predicted based on the first assessment of consciousness. Because EPs have been shown to be of predictive value in the acute phase after the injury, we hypothesised that EPs would also be able to predict outcome in the post-acute phase. It turned out that initial VEP latencies, especially P2 latency, were able to predict long-term outcome, determined by the DRS and GOSE two years after the end of the treatment. VEP amplitudes, especially for the N3 component (N3 amplitude versus baseline and P2-N3 amplitude), predicted the level of consciousness at the end of treatment and long-term outcome assessed with the GOSE. BAEP latencies did not predict outcome.

As far as we are aware, this is the first study in which VEPs were found to be of predictive value in the post-acute phase in vegetative patients. Guérit and colleagues (e.g., Guérit, 2005; Guérit et al., 1993) have already mentioned that the rare use of VEPs in the acute phase is undeserved. VEPs seem to be especially useful in the acute phase when SSEPs are imperfect, in which case the VEPs can be used to give further insight into the prognosis for a patient. This seems to be true for the post-acute phase as well. Admittedly, we have not been able to demonstrate both specificity and sensitivity of the VEPs for final outcome; we were only able to demonstrate a predictive effect by linear regression. Two factors have limited to draw more definite conclusions about outcome predictability on the basis of VEPs. First, uur patient group was relatively small; this was the consequence of our wanting to study longitudinal effects in patients instead of studying large groups. Secondly, the final outcome of the patients

participating in this study was perhaps somewhat restricted. Most of patients did not regain full consciousness and severe disabilities persisted after the treatment period as well as in the long run. It is possible that the outcome in this patient group showed too little variability to allow more precise predictions. Nevertheless, we feel that these findings certainly warrant further investigation of this important problem.

A few issues related to the difference in predicting outcome in the acute versus the post-acute phase are striking. First, the BAEPs and SSEPs seem to be of more prognostic value in the acute phase than in the post-acute phase. In our study, BAEP latencies did not predict outcome at all. SSEPs could not be scored reliably, but the presence of the different SSEP components was used to calculate the composite scores ISBC, IGCF, and the global score. These composite scored were of great predictive value in the acute phase, especially for traumatic injuries like in the present study (Guérit et al., 1993). However, they seemed of little predictive value in the post-acute phase, in which only the global score was linearly related to long-term outcome. Of course, the reasons for the limited predictability of the composite measures in the post-acute phase could also be influenced by the above mentioned limitations of the present study; the relatively low number of patients and little variability in outcome. On the other hand, these findings may also be taken to illustrate that the acute and post-acute phase may produce different results. The post-acute phase is much less well studied than the acute phase, and we make out a case for correcting that difference.

To summarise, we presented the first study of evoked auditory, somatosensory, and visual evoked potentials in vegetative patients in the post-acute phase after severe brain injury. The EPs did not change as a function of the increasing level of consciousness in individual patients. However, the EPs, especially VEP P2 latency and VEP N3 component amplitude, seemed capable of predicting long-term outcome of these patients.

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Appendix Laboratory norms and IBSC, IGCF, and global scores on Evoked Potentials (Guérit et al., 1993).

Normal limits of peak and interpeak latencies used for the calculation of the indices of global hemispheric functioning (IGHF) and the indices of brain-stem conduction (IBSC).

VEPs		SSEPs		BAEPs	
Peak	***Normal values (ms)***	***Peak***	***Normal values (ms)***	***Peak***	***Normal values (ms)***
I	<49	N13	<16.2	I-III IPL	<2.5
III	<95	P14	<18.9	III-V IPL	<2.15
VII	<245	N20	<23.9	I-V IPL	<4.46

Index of Brain-Stem Conduction (IBSC).

IBSC stage	**1. Mesencephalic**	**2. Ponto-mesencephalic**	**3. Ponto-medullary**
SSEPs			
P14	Normal	Normal	Absent
N20	Delayed or absent	Delayed or absent	Delayed or absent
BAEPs			
Peak I	Normal	Normal	Normal or absent
IPLs	Normal or increase	Peak V absent and/or abnormal I-III IPL	Peaks II or III to V absent

Index of Global Cortical Functioning (IGCF).

Grade	**VEPs**	**SSEPs**	**BAEPs**
0	Normal	Normal	Not considered
1	Increase in peak III latency (<120 ms) Peak VII present	Normal N20, P27, and P45 N60 delayed or absent Frontal P22-N30 complex present	Not considered
2	Increase in peak III latency (> 120 ms) Presence of later activities Peak VII absent	Normal N20 and P27 P45 delayed or absent Frontal P22-N30 complex absent	Not considered
3	The only preserved cortical activity is a delayed peak III	Normal N20 No later parietal activities Frontal complex absent	Not considered
4	Peak I is present and reproducible Later activities persist but are poorly reproducible Peak III absent	No cortical activities (parietal or frontal) P14 persists	Not considered
5	Preservation of the ERP The later portion of the wave-form is flat	Both the cortical activities and the P14 are lost Possible persistence of P13	Null or restricted to peak I

Global patterns, based on the indices described above

Global score	**Characteristics**
I	hemispheric damage without brainstem involvement
II	mesencephalic lesion (primary midbrain and/or pontine dysfunction)
III	transtentorial herniation
IV	brain death

Chapter 4

Autonomic reactivity to sensory stimulation is related to consciousness level after severe traumatic brain injury

Abstract

Objective: To examine the changes in the activity of the autonomic nervous system (ANS) related to recovery to consciousness in the post-acute phase after severe traumatic brain injury (sTBI).

Method: Skin conductance and heart rate reactivity to sensory stimulation were recorded every two weeks for an average period of 3.5 months in 16 adolescent patients, during the assessment of their level of consciousness (LoC), and their cognitive and functional behaviour.

Results: Both heart rate variability (HRV) and skin conductance level (SCL) in reaction to sensory stimulation changed linearly with recovery to consciousness. Indices of HRV and SCL that represent sympathetic activity of the autonomic nervous system (ANS) increased with recovery, whereas indices that represent parasympathetic activity decreased. In addition, we observed a linear increase in sympathovagal balance of the ANS with recovery.

Conclusion: Recovery to consciousness determined by clinical observation in sTBI in the post-acute phase is linearly related to changes in the SCL and HRV during sensory stimulation. ANS reactivity to environmental stimulation can therefore give objective supplementary information on the clinical state of sTBI patients, and can contribute to the decision-making in the treatment policy of unresponsive patients.

Significance: These findings demonstrate that autonomic reactivity can be informative concerning how a severely damaged nervous system reacts to environmental stimulation and how, in a recovering nervous system, this reactivity changes.

Introduction

Severe traumatic brain injury (sTBI) results in high morbidity and mortality rates. A large number of patients experiences long-term or lifelong disabilities caused by sTBI, bringing along major costs for family and society. In the United States the incidence of sTBI is eight times as high as that of breast cancer and thirty-four times that of HIV/AIDS (CDC, 2004). However, research on recovery patterns is scarce, especially when young adults are concerned, who are known to be a group of great risk for sTBI (Finfer and Cohen, 2001; Jennett, 1996).

The clinical recovery pattern after sTBI, including the different levels of consciousness and characteristics of those levels has been extensively discussed (Andrews, 1996; Giacino, 1997; Multi-Society Task Force on Persistent Vegetative State, 1994a; Zeman, 2001). Immediately after severe brain damage the patient usually is in a coma. Patients who do not awaken from coma within a period of about four to six weeks may shift into a vegetative state (Jennett and Plum, 1972; Multi-Society Task Force on Persistent Vegetative State, 1994a), or die. In the vegetative state patients have sleep-wake cycles, autonomic control of blood pressure and respiration are present, while cognitive functioning and consciousness are absent. In some patients the vegetative state is the final outcome. A subgroup of patients may shift into a minimally conscious state (Giacino et al., 2002), also referred to as a low awareness state (Andrews, 1996). Patients then demonstrate discernible but inconsistent evidence of consciousness. This state is often transient but can also be the permanent outcome. When patients react adequately to the environment and when communication is possible (with or without tools), they are assumed to be conscious. The experience of self and the environment, and the stock of knowledge, thoughts and intentions are then present (Zeman, 2001); however, various cognitive impairments might still affect the patient (Multi-Society Task Force on Persistent Vegetative State, 1994a).

In current practice, decisions on consciousness rest principally on clinical observations (Chiappa and Hill, 1998). In the acute phase after TBI, the depth of coma is often determined by means of the Glasgow Coma Scale (GCS, Teasdale and Jennett, 1974). Complementary diagnostic investigation by means of neurophysiological assessment is often performed, but mainly aimed at the diagnosis of the brain damage (haemorrhage, oedema, diffuse swelling, intracranial pressure, epileptic seizures, et cetera). In addition, early neurophysiological methods are sometimes used to predict the clinical outcome (Fischer and Luauté, 2005; Fischer et al., 2004; Guérit et al., 1993; Guérit et al., 1999; Kane et al., 2000; Wardlaw et al., 2002).

In the post-acute phase, observation scales are being used as well, examining the recovery to consciousness by observing behavioural skills, like the Western Neuro Sensory Stimulation Profile (WNSSP, Ansell et al., 1989), the Rancho Los Amigos Scale (Hagen et al., 1972), and the Disability Rating Scale (Rappaport et al., 1982). Yet, during this phase neurophysiological assessment is not always considered to be important.

The main purpose of the present study was to examine whether the behavioural changes in the post-acute phase of recovery after sTBI are reflected in physiological reactivity. If so, the examination of neurophysiological features and changes within these features can give more insight into processes and patterns of recovery during the post-acute phase.

Recently, functional neurophysiological reactivity have been shown in VS and MCS using Event Related Potentials (Kotchoubey et al., 2002; Kotchoubey et al., 2005; Neumann and Kotchoubey, 2004), and using fMRI and PET scans (Boly et al., 2004; Jong et al., 1997; Laureys et al., 2004a; Owen et al., 2005; Schiff et al., 2002; 2005).

It appears that external stimuli (as sounds) can provoke cortical activity in VS (Kotchoubey et al., 2005; Laureys et al., 2000; Owen et al., 2005; Schiff et al., 2002). This activity is often reduced to the isolated activity in some 'cortical islands' (Menon et al., 1998; Plum et al., 1998; Schiff et al., 1999; Schiff et al., 2002), which are not integrated in the total network of information processing. Therefore, it is not certain whether there exists any ability to understand (Robertson and Murre, 1999). Results on PET showed that the brain metabolism in VS is reduced with 50% when compared to a healthy brain (Laureys et al., 2002; Laureys et al., 1999). In addition, brain metabolism in VS in different areas is not mutually related, because of the presumably disconnection between the different brain areas (Boly et al., 2004; 2005; Laureys et al., 1999; 2002). Postmortom research showed that in VS often a structurally normal cortex existed (Adams et al., 2000), however, without any connection with other areas like the thalamus.

In MCS the associative brain areas (secundary and tertiary) are active as a response to external stimulation as sound or pain (Boly et al., 2005). These areas are necessary for the conscious perception of stimuli (Baars et al., 2003). In some studies it was found that brain activity in MCS as a response to sound and pain stimulation was equal to a healthy control group (Laureys et al., 2004b; Schiff et al., 2005).

We specifically examined the reactivity of the autonomic nervous system (ANS) to environmental input through different sensory modalities during the recovery from a vegetative state to consciousness. Measurements of the ANS can give insight into mental activity related to the perception and processing of environmental stimulation even in the absence of observable behaviour (Öhman et al., 2000). Measuring the function of the ANS in patients with sTBI may be especially informative. According to Plum and Posner (1980), preservation of arousal is required for recovery to consciousness, because conscious behaviour depends on the continuous interaction between cortical systems and the subcortical activating mechanisms (the noradrenergic and cholinergic reticular activation system). Since arousal is mainly mediated by the ANS, we expected that recovery of consciousness is related to, or even dependent on the functionality and integrity of the ANS.

Spectral analysis of heart rate variability (HRV) and the assessment of skin conductance level (SCL) allowed us to probe the functioning of the sympathetic and parasympathetic branches of the ANS separately. Changes in SCL are influenced primarily by

sympathetic elicitation of sweat secretion (Boucsein, 1992). Slow variations of the heart rate mainly reflect the influence of homeostatic control processes, mediated by the sympathetic branch of the ANS (Berntson et al., 1997). More rapid fluctuations reflect processes related to blood pressure control predominantly, but not exclusively, by the sympathetic branch of the ANS (Akselrod et al., 1981). Very fast fluctuations are related to respiratory activity, primarily controlled by the parasympathetic branch of the ANS (Akselrod et al., 1981; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). In addition, the sympathovagal balance can be examined using HRV (Malliani et al., 1998; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

In our study, adolescents suffering sTBI were admitted to an 'Early Intensive Neurorehabilitation Programme'. Since 1987 the Rehabilitation Centre Leijpark offers this programme for children and young adults in a vegetative or minimally conscious state after acquired brain injury. The rationale of this program is that sensory stimulation and an enriched environment leads to better and faster recovery after sTBI (Rosenzweig and Bennett, 1996). The effect of this programme is not yet demonstrated, however, Eilander et al. (2005b) showed that patients who participated in this programme had a more favourable outcome than predicted by 'The Multi-Society Task Force on Permanent Vegetative State' (Multi-Society Task Force on Persistent Vegetative State, 1994b).

To learn more about the recovery processes during the rehabilitation programme, we studied the activity of the different branches of the ANS during a sensory stimulation protocol (WNSSP; Ansell et al., 1989).

Several studies reported on HRV and SCL in TBI patients, but virtually all were performed in the acute phase and in adult patients. Comatose TBI patients in the acute phase show very low HRV (Lowensohn et al., 1977). An increase in the sympathovagal balance has been found in patients who were recovered from a comatose state in the acute phase (Hildebrandt et al., 1998). Higher sympathetic, and lower parasympathetic activity were seen with better scores on the GCS (8-10). Recently, Su et al. (2005) compared HRV with severity of the brain damage. It was shown that in the more severely brain-damaged patient groups both sympathetic and parasympathetic activity was lower when compared to less severely brain damaged patient groups, and to a healthy norm group.

Electrodermal reactivity to auditory stimuli is lower or even absent in sTBI patients in a vegetative state compared to healthy controls (Turkstra, 1995). Higher electrodermal activity can be seen in patients recovering from the vegetative state (Turkstra, 1995), and with higher scores on the GCS (8-10)(Hildebrandt et al., 1998). Only one study reported on HRV in the post-acute phase in which four adult sTBI patients were compared with matched controls (King et al., 1997). These patients showed lower power in all frequency bands of the heart rate spectrum compared to the controls.

We are not aware, however, of any study in which longitudinal measurements of HRV and SCL is performed in the post-acute phase during recovery to consciousness. In the present report the relation is investigated between the reactivity of the ANS to sensory stimulation, and behavioural changes during the recovery to consciousness and with cognitive recovery of the sTBI patients. It was expected that with the recovery to consciousness patients would become more aroused during the stimulation sessions. Environmental stimuli normally lead to a higher activity of the sympathetic and a lower activity of the parasympathetic nervous system to environmental stimuli: when the sympathetic activity goes up, the parasympathetic activity goes down (Berntson et al., 1991). Following this pattern, the sympathovagal balance during environmental stimulation would increase with recovery to consciousness as a consequence of reciprocal sympathetic activation (Berntson et al., 1991).

Methods

Participants

Sixteen patients with sTBI who admitted to the rehabilitation programme between January 2001 and May 2002 were included in the study (Table 1 presents the patients' details; see also Appendix 7: patient 1 to 16). Inclusion criteria for participation were: age between 17 and 26 years, no mechanical ventilation, and time between injury and admission no longer than six months. Ten (61.1%) were male. Age at the time of the injury ranged from 17.5 to 2.5 years (M = 21.5 years; SD = 3.0). Time since injury at admission was at least four weeks (M = 2.3 months; SD = 1.6). The major cause of TBI was a traffic accident (94,4%)(see the table in Appendix 7 for patients' details). All patients participated in this study following informed consent given by a parent, a legal representator, or partner. The duration of the patients' participation in the program ranged from 1.1 to 6.4 months (M = 3.5 months; SD = 1.4), depending on their recovery rate. The study has been approved by the METOPP (a Dutch Medical Ethics Committee for Research with Patients).

Table 1
Patients'details

Ptn	Gender	Age	Ms	iGCS	IGCS	T1	T2	T3	Primary damage*	Secondary damage*	Location (l= left / r= right)*	LoC 1	LoC 2	DRS cat	GOSE	T4
1	F	25;0	2	4	12	14	40	62	punctual haemorrhages, focal lesions (frontal)	diffuse swelling, compressed basilar cisterns	Cortical + Cerebellum r	6	8	6	5	4;7
2	M	23;1	4	6	12	28	64	78	skull fracture, punctual haemorrhages, contusion (left temporal)	high intracranial pressure, diffuse axonal injury	Cortical l	6	7	7	5	4;6
3	M	19;9	7	2t	11	62	62	126	diffuse punctual haemorrhages also in brain stem, diffuse axonal injury	diffuse white matter lesion	Cortical + Subcortical + Cerebellum +Brain stem	4	7	6	4	4;4
4	M	24;1	3	6	8	16	42	76	oedema right parietal and right and left parietofrontal	atrophy	Cortical	2	7	7	5	4;3
5	M	17;1	6	4t	8	25	40	71	intraventricular haemorrhage, contusions mesencephalon	diffuse swelling, compressed basilar cisterns, atrophy	Cortical + Subcortical + Cerebellum r + Brain stem	3	7	6	5	4;2
6	M	20;1	10	8	10	23	69	133	skull fracture, punctual haemorrhages, diffuse axonal injury	focal lesions and diffuse white matter lesion	Subcortical	2	7	6	3	4;3
7	M	17;7	11	7	11	20	39	195	skull fracture, hypoxia, punctual haemorrhages, diffuse axonal injury, contusions left parietal, right temporal and right frontal	diffuse white matter lesion	Cortical + Brain stem	2	8	5	3	4;1
8	M	18;7	8	5	8	11	31	182	skull fracture, oedema, multiple punctual haemorrhages and contusions	diffuse swelling, diffuse white matter lesion	Cortical + Subcortical	2	5	4	3	4;0
9	M	25;0	6	6	7	16	38	80	skull fracture punctual and subarachnoid haemorrhage, contusions right occipital	diffuse swelling	Cortical + Subcortical r + Brain stem	2	8	6	5	4;0
10	M	25;7	3	2t	10	26	59	118	skull fracture, punctual haemorrhages and intraventricular, multiple contusions		Cortical + Subcortical	6	7	5	3	3;7

(*continued on next page*)

Table 1 *(continued)*

Ptn	Gender	Age	Ms	iGCS	IGCS	T1	T2	T3	Primary damage*	Secondary damage*	Location (l= left / r= right)*	LoC 1	LoC 2	DRS cat	GOSE	T4
10	M	25;7	3	2t	10	26	59	118	skull fracture, punctual haemorrhages and intraventricular, multiple contusions		Cortical + Subcortical	6	7	5	3	3;7
11	M	24;1	5	3	8	58	198	77	skull fracture, oedema and subarachnoid haemorrhage, multiple contusions	atrophy	Cortical + Subcortical	1	2	1	1	4;1
12	M	21;3	7	2t	14	57	57	119	skull fracture, anoxia, oedema, and multiple contusions	diffuse swelling, high intracranial pressure	Cortical + Subcortical	5	7	6	4	3;7
13	F	18;1	8	4	8	31	122	108	oedema, punctual and subarachnoid haemorrhages, diffuse contusions	diffuse swelling, high intracranial, pressure diffuse white matter lesions, atrophy	Subcortical + Brain stem	2	2	4	3	3;8
14	M	21;1	3	5	9	16	79	34	skull fracture, oedema, punctual and intraventricular haemorrhages, multiple contusions	ischaemia, diffuse swelling, high intracranial pressure	Cortical + Subcortical	5	8	6	5	3;6
15	M	17;7	9	6	8	21	73	120	skull fracture, multiple contusions and punctual haemorrhages	diffuse swelling	Cortical	5	7	5	3	3;6
16	M	25;1	8	2t	8	16	81	111	skull fracture, left parietal and right frontal subdural haematoma	intracranial pressure, atrophy	Cortical + Subcortical	3	2	1	1	3;4

Ptn = Patient; F = Female; M = Male; Age = Age at injury in years; Ms = Number of measurements with an interval of two weeks; iGCS = Glasgow Coma Scale at admission; IGCS = Glasgow Coma Scale at discharge; T1 = Time at ICU in days; T2 = Time before admission EINP in days; T3 = Program duration RCL in days; *diagnoses based on the medical report in the acute phase; LoC 1 = Level of Consciousness first measurement; LoC 2 = Level of Consciousness last measurement; DRScat = Disability Rating Scale categories; GOSE = Glasgow Outcome Scale extended; T4 = time of outcome after injury in years

Observation Scales

Level of Consciousness (LoC)

For the Level of Consciousness (LoC) a categorisation was used based on literature on terminology and definitions described by 'the International Working Party Report on the Vegetative State" (Andrews, 1996; Royal Hospital for Neuro-disability, 1996). The categorisation describes a comatose state, three vegetative presentations, three non-vegetative presentations, and a conscious state (see Appendix 3 for the classification scheme in detail).

Preliminarily examination of this observation scale showed high reliability and validity (Eilander et al., 2005a). The inter-observer correlations on the PALOC-s varied between 0.85 and 0.94. The intra-observer correlations varied between 0.95 and 0.96. The inter-observer agreement scores (Cohen's weighted Kappa) varied between 0.82 and 0.95. The intra-observer agreement scores varied between 0.94 and 0.95. The correlations with the WNSSP varied between 0.88 and 0.93, and with the DRS, the correlations varied between 0.75 and 0.88 (Eilander et al. Submitted).

Western Neuro Sensory Stimulation Profile (WNSSP)

Cognitive and communicative functioning was assessed using the WNSSP (Ansell et al., 1989). The WNSSP was specifically developed to assess the cognitive status and communicative performance in severely impaired head-injured patients. The WNSSP consists of 33 items that assess a patient's arousal and attention, expressive communication, and response to auditory, visual, tactile, and olfactory stimulation. Six subscales (arousal and attention, auditory comprehension, visual comprehension, visual tracking, object manipulation, and expressive communication) and four additional observations (response to sound, speech, smell, and touch) have been delineated which assess specific aspects of a patient's behaviour and provide a means for evaluating a patient's pattern of response. The total score ranged from 0 to 113 (the higher the better). See Appendix 4 for a description of the WNSSP.

Stimulation paradigm

The stimulation was provided according to the WNSSP. It was attempted to perform this stimulation as standardized as possible, using the same stimuli, stimulation order and stimulation intensity during every measurement (see Appendix A in this chapter for the exact stimuli).

Disability Rating Scale (DRS)

Changes in arousal and consciousness, and in the cognitive, functional, and psychosocial areas were examined using the DRS (Rappaport et al., 1982). The DRS is a quantitative instrument with a continuous 30-point scale for assessing the disability of sTBI patients. It reflects changes in arousal and awareness, and in the cognitive, functional, and

psychosocial areas. The scale consists of eight items arranged over four categories: 1) arousability, awareness, and responsivity (similar to GCS) 2) cognitive ability for self-care activities, 3) level of dependency, and 4) psychosocial adaptability. Only the total DRS score was used in this study. The lower the total DRS score the fewer the disabilities, ranging from death (score 30) to no disability (score 0). See Appendix 4 for a description of the DRS.

Long-term outcome

To determine the long-term functional outcome, the DRS (Rappaport et al., 1982), well as the Glasgow Outcome Scale Extended (GOSE) (Wilson et al., 1998) were used.
To make the two scales more comparable, the DRS was reduced to 8 categories and is referred to as DRScat (Rappaport et al., 1982): 1=death (score 30), 2=vegetative state (score 22-29), 3=extremely severe disabled (score 17-21), 4=severely disabled (score 12-16), 5=moderately severe disabled (score 7-11), 6=moderately disabled (score 4-6), 7=mildly to partially disabled (score 1-3), and 8=no disability (score 0). See Appendix 5 for a description of the DRScat.

The GOSE is an extension of the Glasgow Outcome Scale (GOS)(Jennett et al., 1981). The GOSE is a one-item rating scale including eight outcome categories (from 'dead' to 'upper good recovery') and can be administered through a structured interview. Compared to the GOS, the GOSE has been shown to be more sensitive to changes in mild to moderate TBI (Wilson et al., 1998). The GOSE consists of eight items: 1=death, 2=vegetative state, 3=lower severely disabled, 4=upper severely disabled, 5=lower moderately disabled, 6=upper moderately disabled, 7=lower good recovery, 8=upper good recovery. The GOSE was administered in a structured interview as proposed by (Wilson et al., 1998). See Appendix 6 for a description of the GOSE.

Psychophysiological Recordings

Heart rate was measured using three disposable Ag-AgCl electrodes (with a contact area of 15 mm) placed on the sternum and the precordial position V6 (Mulder, 1992). The reference electrode was placed under the right clavicle. The inter beat intervals (IBIs) were stored on a personal computer, using an IBI-trigger which detected the R-waves of each heartbeat with a temporal resolution of 1 ms. Skin conductance, expressed in microSiemens (μS), was recorded from the thenar and hypothenar eminences of the non-dominant hand. Two Ag-AgCl skin electrodes (contact area of 8 mm) were attached, filled with an electrolyte consisting of 0.05 M NaCl in a unibase cream medium (Boucsein, 1992). An electric circuit applied a constant voltage of 0.5 V. Raw skin conductance values were digitised at a rate of 10 Hz, and stored on a personal computer.

Experimental Procedure

Two days after a patient was admitted to the rehabilitation programme the first measurement took place. Measurements were repeated every fourteen days. Dependent on

their condition, patients were examined either sitting in upright position in a bed, or sitting in a wheel chair in a quiet room with a constant temperature (23°C ± 1). Measurements were always recorded at the same time of the day (from 3:00 to 4:00 p.m.), immediately after the afternoon resting period.

First, a 3-minute baseline recording of physiological rest-activity was performed (mean duration: 181.4s ± 14.3s). Then, the WNSSP was administered, and physiological reactivity during the stimulation was recorded (mean duration: 913.9 ± 234.6). After the stimulation, a second 3-minute rest period was measured (mean duration: 181.8 ± 5.6 s). A neuropsychologist scored the patients' behaviour according to the observation scales: LoC, DRS, and WNSSP. This assessment was performed every two weeks by the same neuropsychologist until the patient was no longer qualified for the rehabilitation programme. The programme was ended when a) a patient was qualified for further rehabilitation because of recovery of consciousness, b) a patient did not show any recovery during the programme, and therefore was indicated for a nursing home, or c) a patient deceased. These different recovery courses lead to a variation in time span for the patients' participation in the experiment, and in the number of measurements. In addition, patients sometimes could not participate because of their medical condition.

Long-term outcome was determined using the DRScat and GOSE scores at least 3.4 years after the injury (M=4, SD=0.4, see table 1 for the exact time intervals). A rehabilitation physician performed the interviews by telephone with a close relative of the patients (partner or parent).

Analyses

Data Analysis

Recordings were divided into three epochs, representing the first resting period, the stimulation period, and the second resting period. Artefacts in the IBI series were detected by outlier analysis based on the mean and standard deviation of the series (Berntson et al., 1995). These parameters were adjusted for each patient (and each measurement) individually, and based on visual inspection of the whole series. Outliers were deleted from the original series and replaced by values resulting from the application of a cubic spline function. IBIs were then converted to a real-time base at 2 Hz, detrended, tapered with a 10 percent cosine window, and then transformed into the frequency domain (Berntson et al., 1995).

Mean values for the power density in absolute values of power (milliseconds squared) were calculated separately for the LF (≤ 0.04 Hz), the MF (0.04 – 0.15 Hz), the HF (0.15 – 0.40 Hz), and total power (TP ≤ 0.40). Because the raw power values are influenced by the length of the data series, which varied in our administration of the WNSSP, we only report on the power in normalised units (n.u.), separately for the MF (MFn.u.: MF / [TP-LF] x 100) and HF (HFn.u.: HF / [TP-LF] x 100). Sympathovagal balance was calculated as MF/HF (Task Force of the

European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). SCL was determined by averaging all data samples of each of the three intervals. This value was referred to a calibrated baseline, which was set at the start of each measurement. Voltages were converted to microSiemens (μS = R [calibrated voltage / averaged voltage] * 1000kOhm).

Statistical analyses

The changes on the observation scales were examined by comparing the first and the last measurement for each patient, using the Wilcoxin matched-pairs signed-ranks test in the statistical package SPSS 12.0.1 statistics of behavioural indices of recovery and outcome were calculated.

The longitudinal effects were examined in SAS 8.1, using a mixed-model analysis, with a compound symmetry covariance structure. Mixed-effects models use all available data, can properly account for correlation between repeated measurements on the same subject, have greater flexibility to model time effects, and can handle missing data more appropriately (Guerguieva and Krystal, 2004; Keselman et al., 2001; Lui, 2005). In addition, mixed-effects models can be used to model data of ordinal level. Individual trend-analyses were performed and the mean trend-analysis for all patients was determined (see Francis et al., 1991), to examine the shape of the relationship between the dependent variable and the levels of the independent variable. The intercept and the linear (first degree polynomial), quadratic (second degree polynomial) and cubic (third degree polynomial) effects were estimated. For each parameter the strongest effect was reported in the results.

All neurophysiological measurements were analyzed both dependent of time (ordinal measurement) and dependent of the different scores on the observation scales (LoC, DRS, and WNSSP). The individual subjects, ordinal measurement number, and the scores on the observational scales were included as random factors in separate analyses.

A repeated measurement analysis of variance in SAS 8.1 was used to assess the immediate effects of administering the WNSSP. Per patient a mean score was calculated for each resting period (before and after the WNSSP) over all their participated measurements. Overall differences between the two resting periods were analysed, as well as the changes within these differences over time and during recovery.

Results

Behavioural indices of recovery

A maximum of 14 repeated measurements were collected. All patients participated in the first measurement. Fig. 1 shows the amount of patients per measurement and table 1 shows the amount of measurements per patient.

At admission, the patients' average LoC was reflexive vegetative (mean score 3.5).

The average LoC increased to the inconsistent minimally conscious state (mean score 6.2) at discharge (Z = -3.28, P < 0.01). DRS scores changed from the level of complete dependence, but yet showing some signs of arousability, awareness, and responsivity (mean score 22.1), to the level in which the ability for self-care activities, but also independency was present (mean score 13.8) (Z = 3.31, P < 0.01). WNSSP scores changed from an average ability to localize and to follow environmental stimuli (mean score 34.2), to the ability to respond to and to perform simple commands (mean score 89.1) (Z = - 3.36, P < 0.01).

As can be seen in figure 1 and table 2 there was a marked fall-off in the number of patients who underwent the sequential measurements. This irregular distribution of measurements was due to the differences in recovery rate: patients who showed a fast recovery to consciousness were already indicated early for further rehabilitation. In the contrary, the patients who recovered slowly participated in the programme longer. Some of the patients did not show recovery to consciousness, and were indicated for a nursing home. The decision-making on the patients' discharge and follow up destination was influenced by the opinions of relatives or partners, and by waiting lists. In addition, sometimes a measurement could not be performed because of sickness of the patient (e.g. fever).

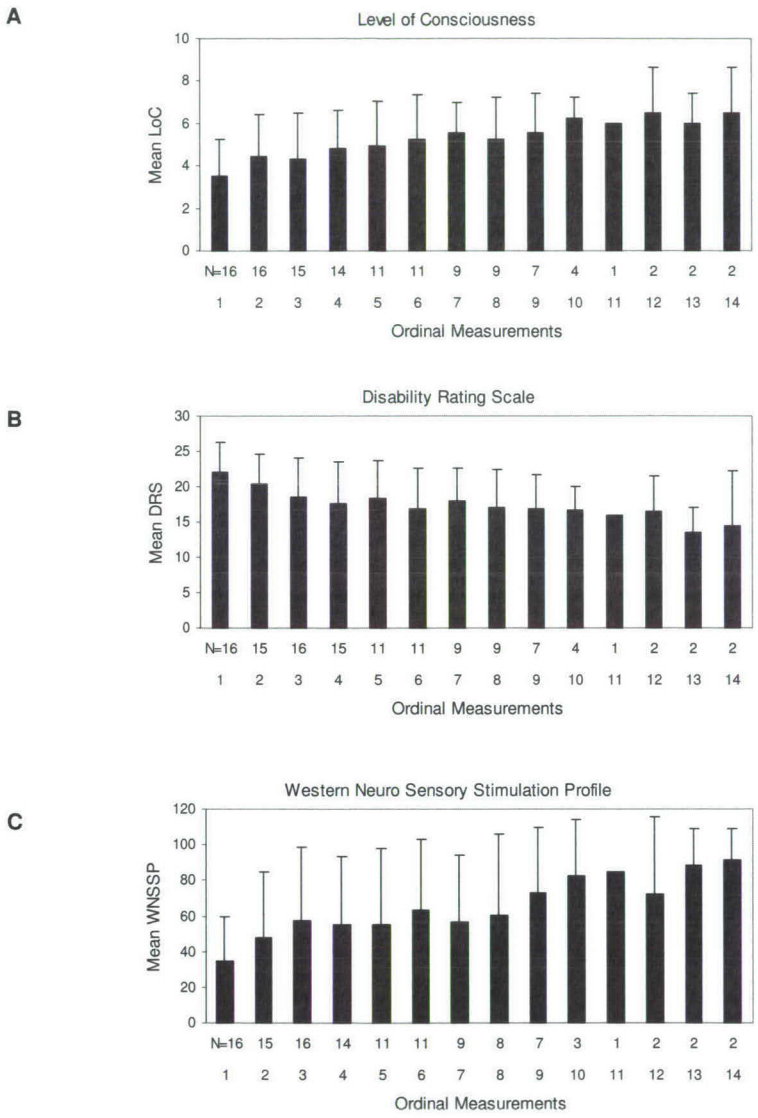

Figure 1. Behavioural indices of recovery. Means and standard deviations over ordinal measurements, which were performed every two weeks, and amount of patients (N) for each measurement. **A**. Level of Consciousness. **B**. Disability Rating Scale. **C.** Western Neuro Sensory Stimulation Profile.

Table 2. Distribution of Levels of Consciousness over the ordinal physiological measurements

Patients	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Measurements																
1	6	6	4	2	3	2	2	2	2	6	1	5	2	5	5	3
2		6	3		3	4	3	3	4	6	1	6	3	7	6	2
3	8	7	5	6	2	3	2	3	5	7	2	6	2	8	5	2
4		7	6	7	5	5	4	3	6		2	6	2		6	2
5			7		7	4	3	3	7		2		2		6	
6			7		7	5	4	4	8				2		7	2
7			7			6	5	5				7	3		7	4
8						6	5	5				6	2		6	2
9						7	5					7			7	2
10						7	6									
11																
12							8	5								
13							7									
14							8									
Total Ms	2	4	7	3	6	10	13	13	6	10	5	9	8	3	9	8

Overall, these data indicate an improvement trend during the programme for LoC, the DRS, and the WNSSP. From the total patients, three patients were still vegetative during the last measurement. These three patients had deceased in the long-term follow up measurement. The patients who eventually recovered to consciousness after the rehabilitation programme still showed disabilities about 3.4 to 4 years after their injury. Two patients were 'mildly to partly disabled' according to the DRScat. Six patients were 'lower moderately disabled' according to the GOSE (see table 3 for the descriptive statistics for the first, the last measurement, and the long-term outcome of all patients).

Table 3 Descriptive statistics of the first and the last measurement, and of the long-term outcome

	First Measurement			Last Measurement			Long-term Outcome	
	LoC	DRS	WNSSP	LoC	DRS	WNSSP	DRScat	GOSE
Mean (SD)	3.5 (1.8)	22.06 (4.2)	34.3 (25.7)	6.2 (2.2)	13.8 (6.4)	89.1 (40.6)	5 (1.8)	3.6 (1.4)
Median	3	23.5	24.5	7	11	109.5	6	3.5
Min-Max	1-6	14-29	0-91	2-8	6-24	8-113	1-7	1-5

LoC: Level of Consciousness; DRS: Disability Rating Scale; WNSSP: Western Neuro Sensory Stimulation Profile; DRScat: Disability Rating Scale categories; GOSE: Glasgow Outcome Scale Extended

Psychophysiological correlates of recovery

Changes in heart rate variability and skin conductance level over time: longitudinal measurements

The MFn.u. increased linearly over time (F (1,86) = 5.22, $p < 0.05$), whereas the HFn.u. decreased linearly (F (1,86) = 4.84, $p < 0.05$). The MF/HF ratio also showed a positive linear trend over the 14 measurements (F (1,86)= 5.68, $p < 0.05$). The SCL showed a cubic trend (F (1,83) = .95, p = < 0.05). After an increase during the first four measurements, SCL slightly decreased to the tenth measurement. After this a slight increase can be observed.

Changes in heart rate variability and skin conductance level in relation to the observation scales: longitudinal measurements

See Fig. 2 for the mean HRV (MFn.u., HFn.u., and MF/HF) and the mean SCL for each score on the observation scales. Relations were found between the scores on the observational scales with the HRV and the SCL.

The MFn.u. linearly increased with LoC (F (1,86) = 24.51, $p < 0.001$), and with scores on the WNSSP (F (1,86) = 26.47, $p < 0.001$), whereas it decreased linearly with scores on the DRS, (F (1,86) = 21.99, $p < 0.001$). Together, these data show that a linear increase in the MFn.u. was associated with better scores on all observation scales.

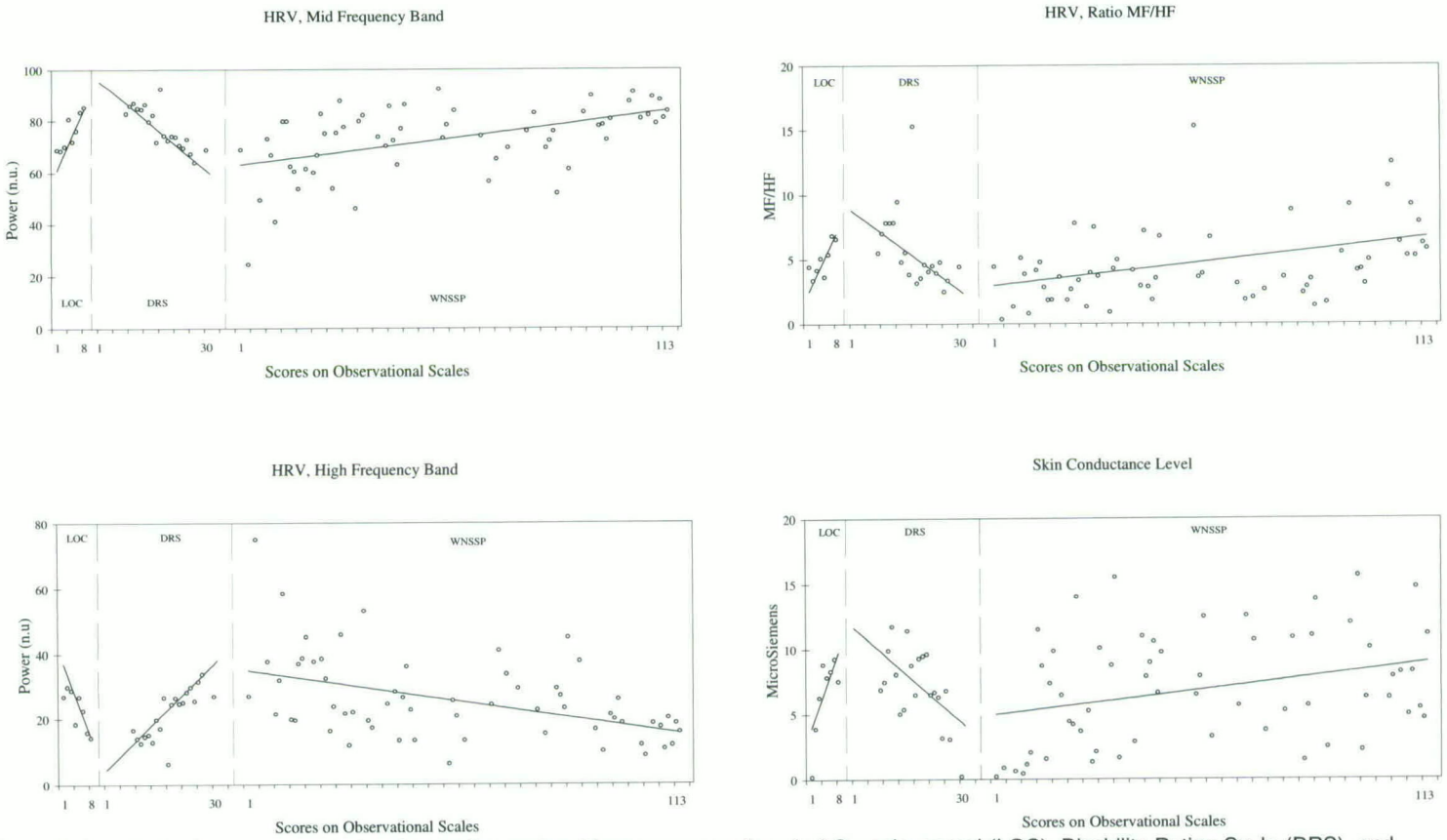

Figure 2. Longitudinal measurements for observation scales: Mean scores on 'Level of Consciousness' (LOC), Disability Rating Scale (DRS), and Western Neuro Sensory Stimulation Profile (WNSSP), for: (a) Mid Frequency band in normalized units. (b) High Frequency band in normalized units. (c) Ratio MF/HF: Level of Consciousness. (d) Skin Conductance Level.

The HFn.u showed opposite effects to the MFn.u. With higher LoC and higher scores on the WNSSP, the HFn.u. decreased linearly (respectively, F (1,86) = 22.36, $P < 0.001$; F (1,86) = 24.00, $P < 0.001$. A linear increase of the HFn.u. was observed with decreasing scores on the DRS (F (1,86) = 19.90, $P < 0.001$). In sum, a decrease in the HFn.u. was related to better scores on all observation scales.

The MF/HF ratio showed resembling patterns as were found for MFn.u. It showed positive linear trends related to increasing scores on LoC and WNSSP, and decreasing scores on the DRS (respectively, F (1,86) = 13.41, $P < 0.001$; F (1,86) = 13.43, $P < 0.001$; F (1,86) = 11.74, $P < 0.001$). In sum, a linear increase in MF/HF was found with better scores on all observation scales.

SCL also increased with better scores on the observation scales. A positive linear trend was found for SCL related to an increasing LoC (F (1,84) = 12.66, $P < 0.001$), to increasing scores on the WNSSP (F (1,84) = 7.99, $P < 0.01$), and to decreasing scores on the DRS (F (1,84) = 8.51, $P < 0.01$).

Taken together, these results show that the sympathetic activity (SCL, and to a lesser extent MFn.u.) increased with recovery, whereas parasympathetic activity (HFn.u.) decreased with recovery. As a consequence, sympathovagal balance (MF/HF) increased with recovery to consciousness.

Immediate effect of administering WNSSP

Differences in autonomic reactivity between the first and the second resting period were found for all measurements. Compared to the first resting period, during the second resting period the MFn.u. was higher (F (1,15) = 14.18, $P = 0.002$) and the HFn.u. was lower (F (1,15) = 14.68, $P < 0.002$). In addition, the MF/HF ratio and the SCL were higher in the second resting period (F (1,15) = 6.32, $P = 0.02$; F (1,14) = 7.08, $P = 0.02$).

These results show that after the stimulation period, sympathetic activity was higher and the parasympathetic activity was lower as compared to the situation before the stimulation period. A longitudinal trend was only found for the sympathovagal balance over measurements (F (1,85) = 4.93, $P < 0.05$). For the other variables no trends were found: the differences between the two resting periods remained equal for each (longitudinal) measurement ($P_s > 0.05$), as well as during recovery ($P_s > 0.05$).

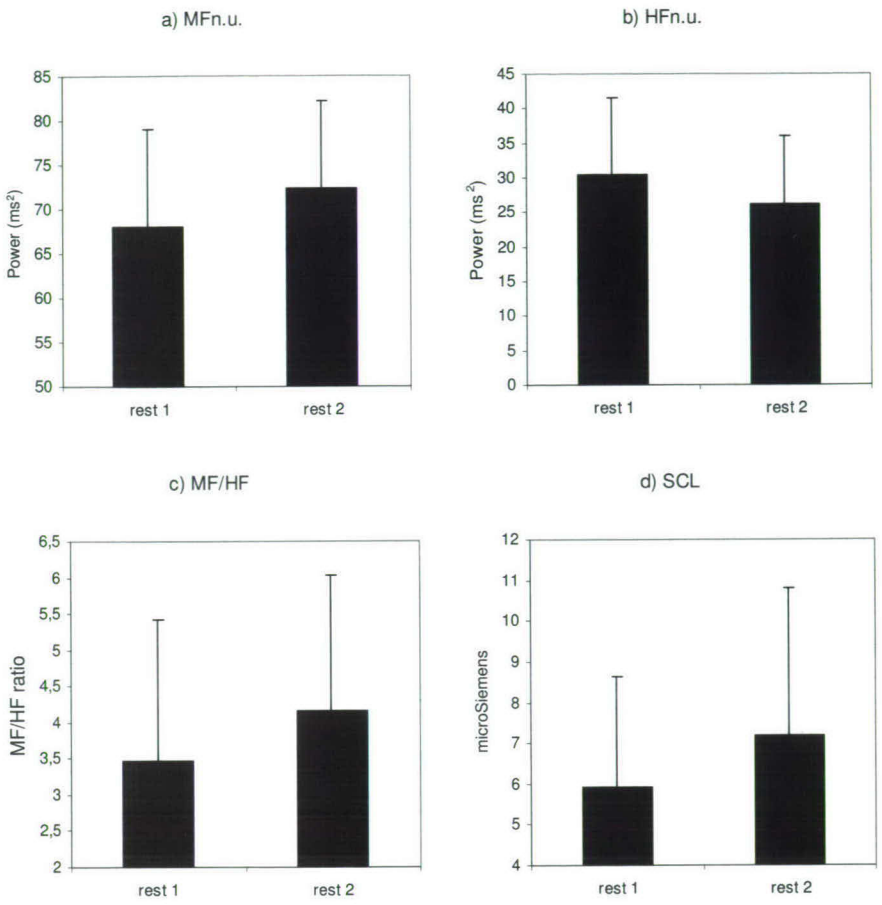

Figure 3. Effects of administering the WNSSP, a comparison between the pre and post rest periods (means and standard deviations): (a) Mid Frequency band in normalized units. (b) High Frequency band in normalized units. (c) Ratio MF/HF. (d) Skin Conductance Level.

Discussion

The activity of the ANS in adolescents with sTBI in the post-acute phase was examined during sensory stimulation. The changes in the reactivity of the ANS during each administration of the WNSSP were examined, as well as the longitudinal changes related to recovery in the post-acute phase. We related the longitudinal changes in ANS activity to the recovery of

consciousness. The results of our study are clear-cut: changes in autonomic reactivity during recovery were linearly related to recovery to consciousness.

The reactivity of the sympathetic branch of the ANS is best reflected in the SCL (Boucsein, 1992), which showed a cubic trend over time, and a linear increase when related to the observational scales. It appears that sympathetic reactivity increases with recovery from the vegetative state to consciousness, and with better performance on the DRS and the WNSSP.

The spectral analysis of HRV provides insight into the sympathovagal balance, as well as the health and functioning of the ANS. The MF is largely attributable to sympathetic nervous activity (Akselrod et al., 1981; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Therefore, the increase of the MFn.u. could reflect an increased sympathetic reactivity. Since the HF is indicative of vagal outflow (Akselrod et al., 1981; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996), the decrease of the HFn.u. component of HRV can be interpreted as a sign of decreased parasympathetic reactivity. As a result, a clear increase in sympathovagal balance (MF/HF) by means of reciprocal sympathetic activation was found.

We conclude that sympathetic reactivity increased and parasympathetic reactivity decreased during recovery from the vegetative state to consciousness in adolescents, after sTBI. Our results in the post-acute phase resemble and extend previous results in the acute phase. For instance, Hildebrandt et al. (1998) found the same pattern in adult patients recovering from a comatose state (defined by a GCS of 8-10) within the acute phase (Hildebrandt et al., 1998). In these patients, MF, SCL, and LF/HF were higher in patients scoring better on the GCS. In addition, recovery in the acute phase is related to an increase in SCL, hence to increased sympathetic reactivity (Turkstra, 1995). It appears that the recovery of ANS function and integrity is an important first step for recovery to consciousness. The DRS scores reveal that most of the conscious patients were still severely disabled at the end of the rehabilitation programme, and three to four years after their injury.

A second unequivocal result from the present study was that ANS reactivity was different after the administration of the WNSSP, and that this difference neither changed over time nor with recovery to consciousness. This could be an important finding in the light of the current paucity of methods for an accurate diagnosis of a non-responsive patient: even when no overt behaviour can be observed, physiological reactivity to environmental stimulation could already be detected. Some form of sensory information processing may still be present. The changes in autonomic activity within each measurement resembled the changes in autonomic activity over time and the changes related to recovery. However, only the patients who did recover, and therefore shifted to higher scores on LoC, and the WNSSP, and lower scores on the DRS, showed the longitudinal changes in ANS reactivity. Of course, because there was no control group, it remains uncertain whether these changes in ANS reactivity during recovery were caused by the stimulation, or were the result of spontaneous recovery.

It appeared that during the first period of recovery the parasympathetic part of the ANS was highly activated, accompanied by a very low activity of the sympathetic part. With recovery to consciousness patients became more aroused, as a result of decreasing parasympathetic and increasing sympathetic activity. This pattern of ANS reactivity supports the notion of Plum and Posner (1980): preservation of arousal is required for recovery to consciousness. The increased arousal to environmental stimulation found in our study was not due to increased motor responses. The later vegetative states (LoC 3 and 4) and the transitional state (LoC 5) are characterized respectively by involuntarily movements, and agitated, emotional behaviour. If the results found were caused by purely motor responses we would have found a quadratic trend with increased arousal followed by a decrease in the later LoCs. The hypofunction of the ANS in the acute phase after TBI may be associated the dysfunction of the reticular activation system (Lehrer et al., 1989). The hyperfunction of the ANS when recovering from sTBI may be associated with affected cortical inhibition centres (Lehrer et al., 1989; Plum and Posner, 1980), and thereby releasing reticular and autonomic networks from normal tonic cortical inhibition. For instance higher skin conductance levels but impaired performances were found in TBI patients in comparison to a healthy control group on cognitive tasks (Plum and Posner, 1980).

Recovery of consciousness depends upon the brain's capacity to repair. In most of the patients involved in our study this capacity appeared to be present. It may be that damage to 'higher' cortical structures that regulate and control the ANS such as the anterior cingulate cortex, the insula, and medial temporal lobe structures such as the amygdala and hippocampus (Critchley et al., 2002; Critchley et al., 2003; Matthews et al., 2004), caused the ANS to be dysfunctional after severe traumatic brain damage. In addition, abnormalities in cholinergic and adrenergic functioning may lead to a dysfunction of the ANS. The neurotransmitters involved in autonomic activity have been suggested to be involved in (cognitive) deficits after sTBI (Lyeth, 2001; Salmond et al., 2005). It is possible that the changes in ANS during recovery to consciousness were due to the recovery of these higher cortical structures controlling the ANS, and nuclei releasing the neurotransmitters (e.g. the locus coeruleus and the basal nucleus of Meynert) involved in the ANS. Furthermore, an overacitivity of the sympathetic branch could still exist, caused by a disturbed inhibition regulation of cortical structures.

To draw conclusions on this issue and to rule out the possibility of an overactivity of the sympathetic branch during recovery in the post-acute phase, patients have to be compared with a healthy norm group.

Differences within brain activity in response to environmental stimuli in vegetative and minimally conscious patients in the acute phase are reported previously (Boly et al., 2004; Kotchoubey et al., 2002; 2005; Laureys et al., 1999; 2000; 2004a; Schiff et al., 2002). In our study differences within ANS reactivity were shown both within the vegetative and the minimally conscious state, during recovery to consciousness. These differences appear to be quantitative rather than qualitative. Viewed from the perspective of ANS reactivity, in the post-acute phase recovery appears to be gradually and continuous. This is interesting in the light of the

discussions about the various stages of recovery (Andrews, 1996; Giacino and Whyte, 2005). The eight sublevels of consciousness we used could be of additional information in research concerning direct brain activity, especially for examining the shift from the vegetative into the minimally conscious state. The current research results justify the question whether VS and MCS represent true 'states' or levels. It is plausible that a continuum exists from the deepest level of coma to the highest level of consciousness, which can only be described artificially. When levels need to be used it is advisable to divide the VS and MCS into sublevels. These two diagnoses are definitely not static ones, and recovery goes with slow steps. Sometimes even a slight regression may be seen during the recovery process. A longitudinal within subject design using ERPs, fMRI or PET could give more insight in both the structural and functional changes involving recovery to consciousness.

Our results may be helpful during the rehabilitation of patients suffering sTBI. The ANS activity after a stimulation period does not change with recovery. However, the ANS reactivity during the stimulation changes over time for patients who recover. This might be useable to identify the patients who are recovering: stimulation appears to directly arouse them more and more over time.

Recognizing the possibility for recovery is important for rehabilitation management, as well as for filling the gaps in our understanding of recovery patterns in the post-acute phase. In a preliminary experiment we found differences in phasic skin conductance and heart rate responses between patients who did and did not recover to consciousness (Wijnen et al., 2005). The reactivity of the ANS to the environment may therefore be a promising topic in future research focusing on early recognition of recovery possibilities.

In addition, early recognition of under- or over-activity within the different branches of the ANS could lead to adjustments in the treatment of sTBI patients. The longitudinal measurements over an extended period of time allowed us to follow the individual patients during their stages of recovery, albeit with a limited number of adolescent patients. Future work involving larger groups of patients of different age categories will be aimed at confirming and extending the present conclusions.

Acknowledgements

We would like to thank Yvonne Schuttelaars and Sylvia Melisse for their contribution in collecting the data, Prof. Dr. J.K. Vermunt for his advise on the statistical analyses used, and K.L. Mansfield for a critical review of the paper on its use of the English language. This study is part of a larger evaluation study of the rehabilitation programme 'Early intensive neurorehabilitation for children and young adults in a vegetative or minimally conscious state after severe brain injury'.
This study was financially supported by: Stichting Centraal Fonds RVVZ, Johanna Kinderfonds, CZ groep Zorgverzekeringen, Zorgverzekeraar VGZ, Zorg en zekerheid, Stichting Bio Kinderrevalidatie, and Hersenstichting Nederland. We are grateful to all members (H. van Dall, P.L. Hoenderdaal, J.C.M. Lavrijsen, A.I.R. Maas, A.J.H. Prevo, H. Stroink, A.J.J.M. Vingerhoets and H. van der Vlugt) of the scientific advisory committee of theresearch project for their contribution to the design of this study.

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Chapter 5

Mismatch negativity predicts recovery from the vegetative state

Abstract

Objective: Mismatch negativity (MMN) is an automatic event related brain response, well investigated in the acute phase after severe brain injury: the presence of a MMN is often found to predict the emergence from coma, and the exclusion of shifting into a vegetative state (VS). In the present study MMN was examined during recovery from VS.

Methods: Ten vegetative patients were repeatedly examined every two weeks for an average period of 3.5 months. Amplitudes and latencies were related to the patients' recovery from VS to consciousness, and to a healthy norm group. In addition, MMN was examined on its prognostic value in VS patients, in predicting recovery to consciousness and long-term functional outcome.

Results: With recovery to consciousness MMN amplitudes increased. A sudden increase was seen in MMN amplitude when patients started to show inconsistent behavioural responses to simple commands. At this level MMN resembled the MMN response as was seen in the norm group. In addition, the MMN amplitude and latency during the first measurement predicted the patients' outcome on recovery to consciousness.

Conclusions: With recovery from VS to consciousness the ability to process auditory stimulus deviance increases. A sudden enhance in MMN amplitude preceded overt communication with the environment. This might be indicative for the consolidation of neural networks underlying overt communication. Moreover, MMN can be helpful in identifying the ability to recover from VS.

Significance: MMN can be used to track recovery from the vegetative state in the post-acute phase after severe brain injury. In addition, MMN can be used to predict the ability to recover from the vegetative state.

Introduction

Severe brain injury results in high morbidity and mortality rates. The majority of patients experience long-term or lifelong disabilities, bringing along major costs for family and society. So far there has been limited research concerning the group of young adults, who have the highest risks (Finfer and Cohen, 2001; Jennett, 1996).

Many individuals who sustain severe acquired brain injury experience prolonged or permanent disorders of consciousness. Acute severe brain injury inevitably results in coma, a state of loss of consciousness with the eyes closed, with no sleep-wake cycle (Multi-Society Task Force on Persistent Vegetative State, 1994a). If not resulting in death within a period of three to four weeks, this coma will develop into a vegetative state (VS; Jennett and Plum, 1972), where the patient seems awake but not aware: uncommunicative and unresponsive to the environment. VS is defined as persistent (PVS) as presence for longer than a month (Bernat, 2006). If recovery continues, patients regain minimal responsiveness to external stimuli (minimally conscious state, MCS; Giacino et al., 2002), that eventually may result in full recovery of consciousness and responsiveness. Otherwise, patients may remain for a long time, or even the rest of their life span, in a vegetative or minimally conscious state. In a later stage it may be considered permanent although on clinical rather than temporal considerations (Working party of the Royal College of Physicians, 2003). Once this diagnosis has been made, ethical and legal issues around withdrawal of treatment may arise (Jennett, 2005). The current study focuses on patients who were in VS for at least a month.

In general, one to fourteen percent of the traumatic, and twelve percent of the non-traumatic prolonged comatose patients shift into VS (Multi-Society Task Force on Persistent Vegetative State, 1994a; Multi-Society Task Force on Persistent Vegetative State, 1994b). Fifty two percent of the traumatic and fifteen percent of the non-traumatic vegetative patients do recover to consciousness (Multi-Society Task Force on Persistent Vegetative State, 1994b). Since recovery from VS to consciousness does occur and depends on residual brain capacities, longitudinal research in the post-acute phase within this group is of great importance to understand what underlies.

The diagnosis of VS and MCS are based on clinical observation of behavioural criteria mostly. Several uncertainties stick to this method. First, observational methods depend on the subjective interpretation of behavioural responses, while conscious experience often occurs without behavioural signs. Second, no initial behavioural differences exist between the patients who may recover to consciousness and those who remain permanently vegetative.

To obtain complementary objective information about the level of consciousness in non-responsive patients, the present study focuses on neurophysiological responses during the recovery from VS to consciousness. A longitudinal study was performed in which the Mismatch Negativity (MMN)(Näätänen et al., 1978) was examined.

MMN is generated by the brain's automatic response to physical stimulus deviation from the preceding stimulus in repetitive auditory input, revealing that physical features of auditory stimuli are fully processed regardless whether they are attended to or not (Näätänen et al., 2004). Mismatch Negativity has repeatedly shown to predict outcome after coma (Fischer et al., 1999; 2004; Kane et al., 1993; 1996; Luauté et al., 2005; Morlet et al., 2000). Fischer et al. (1999; 2004) demonstrated that in the acute phase the presence of MMN predicted the exclusion of shifting into PVS. Additionally, Luaute et al. (2005) showed that when MMN was present in comatose patients no patient turned to permanent VS one year after the brain insult. MMN responses have been found in VS and MCS patients, especially when complex tones or musical notes were used (Jones et al., 2000; Kotchoubey et al., 2003; 2005). Additionally, in a study of Kotchoubey et al. (2005) six months after the brain insult clinical improvement was observed more frequently in VS and MCS patients with a significant MMN than in those without the MMN. Up till now researchers have not longitudinally investigated MMN responses during the recovery from VS. The present study reports on longitudinal changes in MMN responses during recovery to consciousness, and on its prognostic value in VS patients.

Methods

Participants

Ten severely brain injured patients (7 were male; age $M = 17.3$, $SD = 4.4$, 8-25 years), who were admitted to an Early Intensive Neurorehabilitation Programme (Eilander et al., 2005) took part in the study between November 2002 and January 2004 (Table 1 presents patients' details; see also Appendix 6: patient 17, and 20 to 28). The duration of the patients' participation in the programme ranged from 1.5 to 5.2 months ($M = 3.5$ months; $SD = 1.03$). Time since injury at admission ranged from 6.2 to 19.4 weeks ($M = 11.6$ weeks; $SD = 3.6$). All but two patients suffered from a traumatic brain injury caused by traffic accidents (see the table in Appendix 7 for patients' details).

A norm group consisted of 16 persons, matched for mean age ($p = 0.6$) and gender (56% were male).

All the patients and the norm group participated in this study following informed consent given by one of the parents or a legal representator (all the patients and norm group aged<16 years), or by themselves (norm group aged ≥ 16). The study has been approved by a medical ethics committee (METTOP).

Table 1 Patients' details

P	Ms	TM	M/F	Age	Cause	Initial CT-scan (s)*	GCS	T1	T2	T3	LoC1	LoC2	LoC-discharge	LOCT-discharge	DRS	GOSE	T outcome
17	2	6,5	M	17,6	traffic accident	Epidural haematoma (right).	2t	72	80	139	4	4	4	217	3	3	3.0
20	4	6,1	M	15,4	traffic accident	Skull fractures, arachnoid haemorrhages, contusion and punctual haemorrhages (right frontal, temporal, parietal), diffuse swelling.	4	33	136	112	5	5	5	204	4	3	2.9
21	3	2,4	M	25,2	traffic accident	Skull fracture, oedema and punctual haemorrhages (cortical), diffuse swelling, and diffuse white matter lesions.	2t	65	64	77	4	7	8	141	6	3	2.7
22	4	2,9	M	8,4	cerebral haemorrhages	Intraventricular and intracerebral haemarrhages, left cortical.	2t	33	81	119	3	7	7	133	7	3	2.6
23	8	1,9	F	18,8	traffic accident	Oedema, ischemia, high intracranial pressure, diffuse swelling.	3	29	49	115	4	7	8	164	4	3	2.4
24	3	4,5	M	17,5	traffic accident	Oedema, intraventricular and intracerebral haemorrhages, focal lesions (subcortical, brainstem), diffuse white matter lesions.	4	13	44	92	4	4	8	136	7	6	2.5
25	7	2,6	M	21,8	traffic accident	Puntual haemorrhages, intraventricular haemorrhage (left), diffuse swelling, diffuse axonal injury.	5	26	71	105	4	4	4	176	3	3	2.5
26	5	2,2	F	15,7	traffic accident	Subarachnoid haemorrhage (right), high intracranial pressure, oedema (right subcortical and brainstem).	4	30	60	99	3	5	8	159	5	3	2.4
27	9	2,9	M	17,2	traffic accident	Intraventricual haemorrhages (bilateral), multiple punctual haemorrhages, Large haemorrhage in basal ganglia, and right frontal, oedema (mainly left perventricular white matter).	3	62	80	157	3	5	5	237	1	1	2.2
28	4	3,6	F	15,2	pneumonia + sepsis shock	Hypodensity in basal ganglia and cortical temporoparietal, anoxia, cortical and cerebellar atrophy, diffuse white matter lesion.	3	57	102	45	3	2	3	147			2.7

P = patient; Ms = participated measurements; TM: time between injury and first measurement in months; F = female; M = male; Age = age at injury; * = diagnoses based on the medical reports of the acute phase; GCS = GCS at admission hospital; t = endotracheal tube; T1 = time at ICU in days; T2 = time before admission RCL in days; T3 = programme duration RCL in days; LoC1 = Level of Consciousness during the first EEG-protocol; LoC2 = Level of Consciousness during the last EEG-protocol; LoC-discharge= Level of Consciousness at discharge; LoCT-discharge = time after injury in days for Level of Consciousness at discharge; DRS = Disability Rating Scale; GOSE = Glasgow Outcome Scale extended; Toutcome = time after injury in years for DRS and GOSE

Level of Consciousness

For the Level of Consciousness (LoC) a categorisation was used based on the definitions described by 'the International Working Party Report on the Vegetative State' (Andrews, 1996), and the Aspen Neurobehavioural Conference (Giacino, 1997; Giacino et al., 1997). The categorisation describes a comatose state, three vegetative sub-states, three non-vegetative sub-states, and a conscious state (see Appendix 3 for the classification scheme in detail).

This classification scale showed high reliability and validity (Eilander et al., submitted). The interrater-reliability (Spearmans' rho) varies between 0.85 and 0.94. The interrater-agreement (Cohens' weighted Kappa) varies between 0.90 and 0.95. The intrarater-reliability is 0.96 and the intrarater-agreement is 0.94. Correlation of the scores of the rated scores with the Western Neuro Sensory Stimulation Profile (WNSSP; Ansell et al., 1989) varies between 0.85 and 0.90, and with the Disability Rating Scale (DRS; Rappaport et al., 1982) between 0.88 and 0.94.

In a second approach this classification was reduced to four levels: level 1 was defined as Coma, the levels 2, 3, and 4 as VS, levels 5 and 6 as MCS, and level 7 and 8 as exitMCS (5, 6) or Conscious State.

MMN data acquisition and analysis

The presented stimuli were 1500 pure tones of 1000 Hz (85%, standard) and 1500 Hz (15%, deviant), with an intensity of 70 dB SPL and duration of 75 ms (rise and fall time 10 ms), delivered binaurally through insert earphones. The interstimulus interval was 500 ms.

Electroencephalographical activity (EEG, sampling rate 2kHz, Common Mode Rejection Ratio > 80 dB) was recorded (BioSemi activeTwo, Amsterdam) using actively shielded electrodes. The total equipment was tested and approved on safety by a Metron QA-90 safety tester in the Tweesteden Hospital (Tilburg, The Netherlands). The electrodes were placed using an EEG-head cap and electrode gel (Parker Signa) according to the 10/20 system, at F3, Fz, F4, C3, Cz, C4, Pz, and Oz, referenced to linked mastoids.

Horizontal EOG was recorded from two electrodes placed at the outer canthi of both eyes. Vertical EOG was recorded from electrodes placed on the infraorbital and supraorbital regions of the two eyes in line with the pupil. EOG artefacts were corrected using a regression procedure (Gratton et al., 1983).

EEG signals were band-pass filtered (0.15-30Hz, 48 dB/octave). The raw data were segmented into 1500 epochs, including a 100 ms prestimulus baseline. Epochs with an amplitude change exceeding ±100 μV at any channel were automatically rejected. ERPs were averaged separately for the standards and deviants. The ERP to standards included the responses to those standards which immediately followed deviants.

After averaging the standard and deviant responses for each measurement and subject the ERPs were filtered between 3 – 30 Hz (Fischer et al., 1999; Morlet et al., 2000). For each measurement in every subject it was visually inspected whether there was N1 in both averaged standard and deviant responses. Difference waveforms were computed by subtracting the averaged ERP elicited by the standard from that of the deviant, and were filtered between 3 – 8 Hz (Fischer et al., 1999; Morlet et al., 2000). For each measurement in every subject MMN was defined as being any negativity differing from zero level within the time window of 100 – 300 ms.

Definition of Outcome

When the patients were discharged from the programme their LoC was determined by the rehabilitation physician, based on the description in table 2, after a discussion with the multidisciplinary treatment team about each patient (see table 2). This LoC is further referred to as $LoC\text{-}_{discharge}$.

Long-term outcome: Disability Rating Scale (DRS) and Glasgow Outcome Scale Extended (GOSE)

To determine the long-term functional outcome, the DRS (Rappaport et al., 1982) as well as the GOSE (Wilson et al., 1998) were administered. The DRS consists of eight items, which can be summed up to values from 0 to 29. A high score on an item indicates a low level of functioning on that aspect. To make the two scales more comparable, the DRS was reduced to 8 categories according to Rappaport et al. (1982): 1=dead (score 30), 2=vegetative state (score 22-29), 3=extremely severe disabled (score 17-21), 4=severely disabled (score 12-16), 5=moderately severe disabled (score 7-11), 6=moderately disabled (score 4-6), 7=mildly to partially disabled (score 1-3), and 8=no disability (score 0).

The GOSE is a one-item rating scale including eight outcome categories and can be administered through a structured interview (Wilson et al., 1998). Outcome categories are: 1=death, 2=vegetative state, 3=lower severely disabled, 4=upper severely disabled, 5=lower moderately disabled, 6=upper moderately disabled, 7=lower good recovery, 8=upper good recovery.

Experimental Procedure

Nine days after a patient was admitted to the programme the first measurements took place. Patients were examined while they were lying in a bed in a quiet room with a constant temperature (23 ± 1 ℃).

Every two weeks the MMN measurement was performed at the same time of the day (between 10:30 a.m. and 11:30 p.m.), as part of an ERP protocol. Brainstem auditory evoked potentials (BAEPs) were also recorded, and they were present in all of the measurements of each subject. In the same week the rehabilitation physician determined LoC.

These assessments were performed until the patient was discharged: a) a patient was qualified for regular rehabilitation because of recovery of consciousness and cognitive abilities, or b) a patient did not show any recovery in a period of at least six weeks during the programme.

The norm group was measured once, in the same position and location, at different times of the day. They underwent the same EEG-protocol as the patients.

Long-term outcome was determined by the DRS and GOSE scores at least 2 years after the injury (M = 2.6, SD = 0.28, see table 1 for the exact time intervals: Toutcome). A rehabilitation physician performed the interviews by telephone with a close relative of the patients (partner or parent).

Statistical analysis

The longitudinal changes of MMN-amplitude, and MMN-peak latency were analysed as a function of LoC using a linear Mixed Model procedure. LoC and the individual subjects were included as random factors. Mixed-effects models use all available data, can properly account for correlation between repeated measurements on the same subject, have large flexibility to model time effects, and can handle missing data appropriately (Francis et al., 1991; Keselman et al., 2001). Mixed-effects models can be used to model data of ordinal level (Gueorguieva and Krystal, 2004).

Mann-Whitney Two Independent Samples tests were used to examine the 'between group effects' for the patient group in the different LoCs and the norm group.

Finally, the predictive value of MMN amplitude and MMN peak latency for outcome was examined, using linear regression analyses and Receiver Operating Characteristic (ROC) analyses.

Results

Behavioural indices of recovery

At admission, the patients' averaged LoC score was 3.6 (± 0.52). At the end of the programme the average LoC score had increased to 5.9 (± 1.9). Five patients reached a conscious level (exit MCS: LoC 7 or 8), 2 patients were still in MCS (LoC 5 or 6), and 3 patients were still in VS (LoC 2-4) at the end of the programme.

The long-term outcome scores on the DRS and GOSE could be obtained for 9 patients, and are shown in table 1. Two to 3 years after the injury the mean score on the DRS was 4.4 (± 2.0). The mean score on the GOSE was 3.1 (± 1.3).

Changes in MMN: longitudinal measurements

Figure 1 shows the MMN-amplitude as a function of LoC when the 8 sublevels were taken into account. With an increasing LoC, the MMN-amplitude became larger, showing a discontinuous pattern over LoCs, F (5, 26) = 6.6, p < 0.0001. A sudden increase in MMN amplitude occurred after LoC 5. Figure 2 shows the accompanying grand averages.

When LoC was divided into three levels (VS, MCS, exit MCS) a significant increase of MMN amplitude was found when patients recovered from the VS to consciousness , F (2, 22) = 7.32, P = 0.004 (Figure 3).

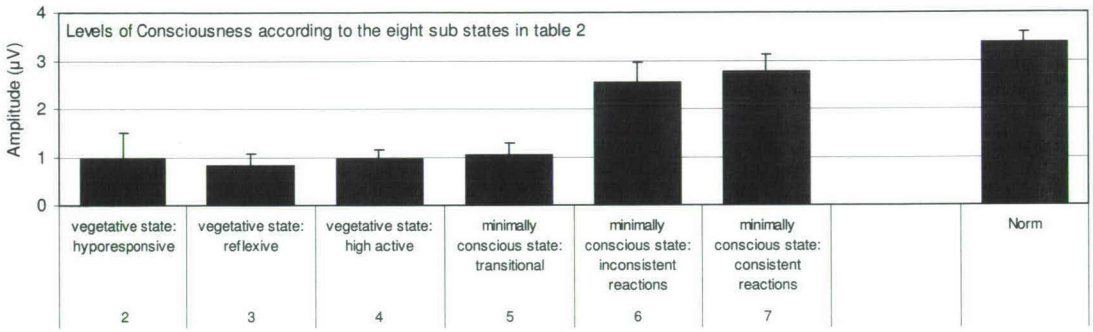


Figure 1. Longitudinal measurements: mean MMN amplitude (Fz) and standard error for each Level of Consciousness according to the levels of Appendix 3 versus the norm group. For number of measurements see table 1.

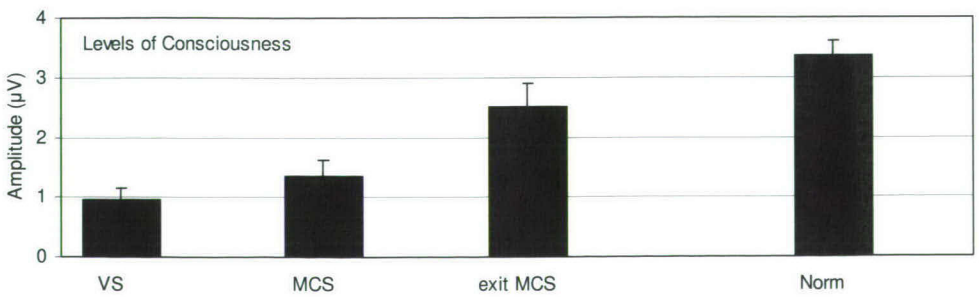


Figure 3. Longitudinal measurements: mean MMN amplitude (Fz) and standard error for Level of Consciousness when divided into three levels: VS, MCS, and exit MCS.

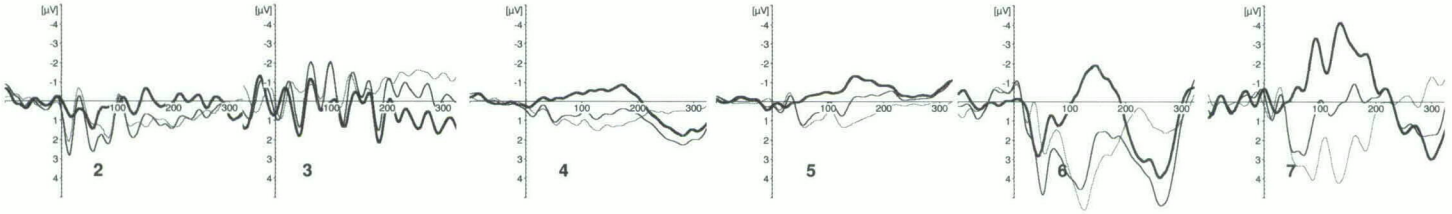
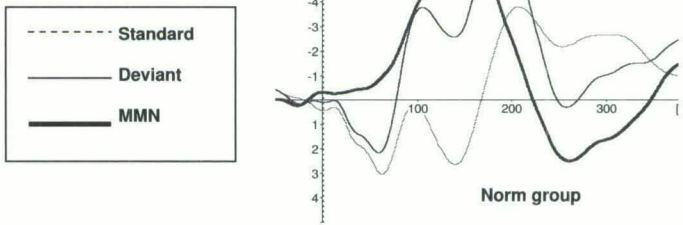


Figure 2. Grand Averages of MMN (Fz-linked Mastoids, 0.15-30Hz, 48 dB/octave) for each Level of Consciousness according to the levels in Appendix 3 versus the norm group. Potentials related to the standard stimuli, potentials related to the deviant stimuli, and the MMN (difference between the deviant and standard).



Although MMN peak latency decreased with recovery, these effects were not significant, both when LoC was divided into 8 and 4 sublevels (respectively $F(5, 36) = 1.07$, $p = 0.40$, $F(2, 38) = 1.75$, $p = 0.20$).

Comparison with the norm group

Group effects for LoC 1, 2 and 8 could not be statistically analysed. No patients were scored at LoC 1 during this study. Only one patient was measured twice in LoC 2, and no patients were measured in LoC 8 (see table 2 for group means and standard deviations). Therefore, analyses were only performed for LoC 3 to LoC 7.

Table 2. Means and standard deviations (in parentheses): peak latency and peak amplitude of MMN (Fz) for each level of consciousness and the norm group

LoC	Measurements	Patients	Latency (ms)	MMN Amplitude (μV)
1 *	0	0		
2	2	1	204 (64)	- 0.9 (0.7)
3	9	5	201 (42)	- 0.8 (0.5)
4	18	7	196 (64)	- 0.9 (0.7)
5	12	4	197 (50)	- 1.0 (0.7)
6	3	2	153 (12)	- 2.7 (0.5)
7	4	3	141 (23)	- 2.9 (1.0)
8 *	0	0		
Norm		16	155 (23)	- 3.4 (1.1)

*No measurements were performed during these levels of consciousness

MMN amplitude within each LoC in the patient group was compared with the MMN in the norm group. Group effects were found for MMN-amplitude. Amplitudes in LoC 3 to 5 were smaller in comparison to the norm group (respectively $U = 2.0$, $p < .0001$; $U = 1.0$, $p < .0001$; $U = 2.0$, $p = 0.002$), whereas LoC 6 and 7 did not significantly differ from the norm (respectively $U = 6.0$, $p = 0.21$; $U = 10.0$, $p = .14$). When LoC was divided into four levels (Coma, VS, MCS, and exit MCS) the patients' MMN amplitude in VS and MCS significantly differed from the norm group (respectively $U = 3.0$, $p < .0001$; $U = 8.0$, $p = .002$). Patients who emerged from MCS did not significantly differ from the norm group any longer ($U = 10.0$, $p = .14$).

Patients' peak latencies at LoC 3 and 5 differed (marginally) from the norm group (respectively $U = 17.0$, $p = .06$; $U = 9.0$, $p = .03$). No differences were found between the norm group and patients at LoC 4, 6, and 7 (respectively $U = 44.0$, $p = .53$; $U = 11.0$, $p = .55$; $U =$

19.0, p = .63). When LoC was divided into four levels (Coma, VS, MCS, and exit MCS) the patients' MMN latency in VS marginally differed from the norm group (U = 61.0, p = .06). Patients in MCS and patients that emerged from MCS did not significantly differ from the norm group any longer (respectively U = 30.0, p = .20; U = 19.0, p = .63).

Predictive value of MMN: relation to the first measurement to outcome

MMN amplitude during the first measurement strongly predicted $LoC\text{-}_{discharge}$ (β = - 0.94, t = - 8.07, p < .0001). The patients with $LoC\text{-}_{discharge}$ < 7 showed smaller MMN amplitudes during their first measurement, and the patients that recovered to $LoC\text{-}_{discharge}$ = 7 or 8 showed larger MMN amplitudes during their first measurement. The LoC score during the first measurement did not predict $LoC\text{-}_{discharge}$ (p_s > .40)(Table 3).

Table 3. MMN peak amplitude, peak latency and LoC during the first measurement, and LoC at discharge of the programme

Patient	LoC_{first}	MMN_{first}		$LoC_{discharge}$
		Amplitude (μV)	Latency (ms)	
1	4	-0.19	248.54	5
2	5	-0.40	251.95	5
3	4	-1.46	156.25	8
4	3	-1.29	173.34	7
5	4	-2.11	154.30	8
6	4	-1.70	168.95	8
7	4	-0.34	399.41	4
8	3	-1.59	228.52	8
9	3	-0.86	208.50	5
10	3	-0.32	238.28	3

A ROC analysis for MMN amplitude at the first measurements showed 100% sensitivity and specificity in predicting outcome at the end of EINP, when a cut-off value of $LOC\text{-}_{discharge}$ < 7 was used (p = .009).

Regression analyses did not show significant results for MMN amplitude during the first measurement in predicting the long-term outcome for DRS and GOSE (p_s > .10). However, the occurrence of MMN amplitude larger than -1μV predicted the DRS score about two years after the injury (p = .02).

See figure 4 for the distribution of the patients' first MMN amplitude compared to their short-term and long-term outcome.

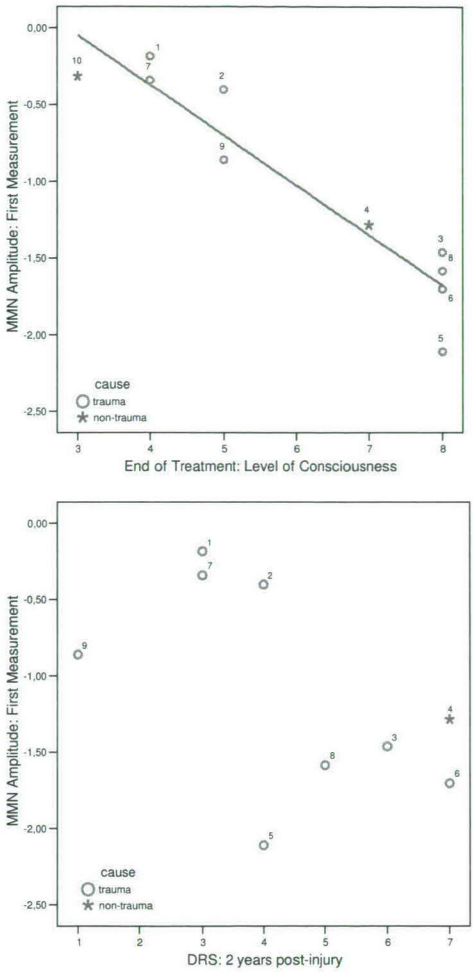


Figure 4. **Predictive value of MMN amplitude during the first measurement**: a) Level of Consciousness at the end of the treatment programme. b) Disability Rating Scale: long-term outcome

In comparison with the amplitude, a less strong prediction was shown for the initial MMN peak latency for $LoC\text{-}_{discharge}$ (β = -0.67, t = -2.58, p = .03)(table 4). Shorter peak latencies were found in the patients that recovered to higher LoC scores. In addition, the ROC analysis for MMN peak latency showed less strong sensitivity and specificity in predicting outcome at the end of EINP (p = .02). No significant results were found for latency during the first measurement in predicting the long-term outcome for DRS and GOSE (p_s > .10).

Discussion

MMN amplitude predicted the level of consciousness, and functional outcome two years after the injury. All patients that ultimately recovered to consciousness already showed higher amplitudes and shorter latencies in VS (first measurement) in comparison to the patients that remained in VS or MCS. A less strong prognostic value was found for the long-term functional outcome. The DRS and GOSE scores reveal that most of the conscious patients were still severely disabled about two years after their injury.

Another striking result was the increased MMN that was demonstrated during the period leading up to the recovery of consciousness. Amplitudes became larger, and reached the healthy levels of a matched norm group. The difference between the patients' states according to electrophysiological data did not exactly correspond to the clinical diagnosis, that is VS versus MCS. Rather, the most important improvement of the electrophysiological status is within the range of minimally conscious states. A sudden increase in MMN occurred within MCS (from LoC 5 to LoC 6) and preceded overt consistent behavioural responses to the environment (LoC 7). Unfortunately, practical issues (discharged from the programme, behavioural problems) lead to the fact that no patients were measured in LoC 8.

Our results on the predictive value of MMN extend the previous results of Fischer et al. (1999; 2004) in the acute phase. In their study MMN was found to predict the awakening from coma and the exclusion of VS. The present study reveals that MMN can give insight in those who do shift in to VS: MMN predicts the recovery from VS to consciousness.

Previous studies already showed residual cerebral function in severely brain-injured patients (Boly et al., 2004; Laureys et al., 2000; Schiff et al., 2005). Differences were found between VS and MCS patients in auditory processing (Boly et al., 2004). Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) showed more significant activity in superior and middle temporal gyri and tighter functional connectivity with other brain areas in MCS patients than was found in patients in VS while they were exposed to auditory stimulation. In addition, some prefrontal activation was shown in MCS patients in a language related task (Schiff et al., 2002).

The PET and fMRI results demonstrated a consistent language-responsive network while the patients showed inconsistent evidence of receptive and expressive language skills. These same regions were earlier found to be involved in the generation of MMN using a topographic event related potential study (Giard et al., 1990). The emergence from MCS is defined by showing reliable and consistent interactive communication or functional use of objects (Giacino et al., 2002; Schiff and Purpura, 2002). The clear enhanced MMN found in our patient group in LoC 6 might therefore be indicative for the consolidation of neural networks underlying consistent interactive communication. This result confirms earlier findings in which neural activity expressed in MMN preceded behavioural learning using a speech related MMN

paradigm (Tremblay et al., 1998). Some learning occurs at a pre-attentive level, and therefore can be assessed in the absence of behavioural responses.

In conclusion, we showed that MMN is a powerful tool in predicting the recovery from VS to consciousness. However, a larger patient group is needed to elaborate on these findings. The predictive value of the MMN may strongly depend on other variables investigated together with the MMN. To predict outcome in future studies using larger samples, some potentially important predictors (such as clinical, demographical, and psychological information) could be included into the prediction model.' that the predictive value of the MMN may strongly depend on other variables investigated together with the MMN. A follow up assessment of outcome is important to draw further conclusions on functional outcome.

Additionally, in future studies a nose-reference would be the optimal choice to provide a MMN (Näätänen et al., 2004; Schröger, 1998). In the current study, however; for practical reasons (e.g. defensive behaviour in the given patient group), linked mastoids were used for reference.

Our results add to the knowledge on differences between and within VS and MCS. The sudden increase in MMN within MCS points out that the eight sublevels of consciousness we used could be of additional information, and that VS and MCS are not static states.

A speech related, topographical MMN study is important to confirm the enhanced MMN amplitude to be preceding overt communication with the environment. A combination of structural and functional assessment (fMRI, PET, ERP) of information processing using words or vowels (Kotchoubey et al., 2001; Kotchoubey et al., 2005) in a longitudinal design might give more insight.

Acknowledgements

This study was financially supported by: Stichting Centraal Fonds RVVZ, Johanna Kinderfonds, CZ groep Zorgverzekeringen, Zorgverzekeraar VGZ, Zorg en Zekerheid, Stichting Bio Kinderrevalidatie, and Hersenstichting Nederland. We gratefully acknowledge the cooperation of the patients and their families on this study. We are grateful to all members (H. van Dall, P.L. Hoenderdaal, J.C.M. Lavrijsen, A.I.R. Maas, A.J.H. Prevo, H. Stroink, A.J.J.M. Vingerhoets and H. van der Vlugt) of the scientific advisory committee of the research project for their contribution to the design of this study.

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Chapter 6

Auditory oddball responses during the recovery from the vegetative and minimally conscious state

Abstract

Objective: The auditory oddball response has been found to be of predictive value for neurological outcome at the early stages of coma. The presence of a P300 has been found to be related with good outcome. Also a frontal negativity at about 350ms (N350) predicted a good outcome in one study. So far, no longitudinal studies are reported on the auditory oddball paradigm during post-acute phase after severe brain injury. In the present study, P300 and N350 responses were studied longitudinal during the recovery from the vegetative state to consciousness.

Methods: The P300 and the N350 were repeatedly examined every two weeks for an average period of 3,5 months in 10 severely brain injured patients. The P300 and N350 of the patients were related to their behavioural changes during recovery from the vegetative state to consciousness, and to a healthy control group. In addition, the ERPs were examined on their prognostic value in the post-acute phase, in predicting recovery to consciousness and long-term outcome about 2 years after the injury.

Results: ERP components were often difficult, if not impossible to score. Therefore, the data were resorted to a description of the averaged data as well as the data of individual patients and measurements as reliably as possible. The healthy control group showed a classical P300 potential. Both the P300 and the N350 in the patients differed from the healthy controls. In the recovered group consistent potentials were found; however, amplitudes were smaller, and there was a delay when compared to the controls. In addition, scalp distribution was slightly more central in patients. Only the N350 was of some predictive value for long-term outcome.

Conclusion: The present study replicated earlier findings that N350 and P300 can be measured in comatose patients, and extended those findings to the post-acute phase, during the recovery from the vegetative state to consciousness. Although no evidence was found that the N350 and the P300 changed as a function of recovery, we did find some evidence that outcome can be predicted from the presence of the N350.

Significance: These findings are important because predicting outcome after severe brain injury is not possible based on behavioural indices alone.

Introduction

Many individuals who sustain severe acquired brain injury experience prolonged or permanent disorders of consciousness. Acute severe brain injury inevitably results in coma, a state of loss of consciousness with the eyes closed, with no sleep-wake cycle (Multi-Society Task Force on Persistent Vegetative State, 1994a). If not resulting in death within a period of three to four weeks, this coma will develop into a vegetative state (VS; Jennett and Plum, 1972), where the patient seems awake but not aware, uncommunicative and unresponsive to the environment. If recovery continues, patients regain minimal responsiveness to external stimuli; the minimally conscious state (MCS; Giacino et al., 2002), that eventually may result in full recovery of consciousness and responsiveness. But patients may also remain in a vegetative or minimally conscious state for a long time, even the rest of their lives.

The diagnoses of the vegetative and the minimally conscious states usually rely on clinical observation of behavioural criteria only. However, this method of arriving at diagnoses is restrained by several uncertainties. First, observational methods depend on the subjective interpretation of behavioural responses, whereas conscious experience often occurs without behavioural signs. Secondly, no initial behavioural differences exist between the patients who recover to consciousness and those that remain permanently vegetative. To obtain complementary objective information about the level of consciousness in non-responsive patients, we initiated a series of studies in which we attempt to explore the neurophysiological correlates of recovery from the vegetative state to consciousness. The studies consist of two distinguishable parts. First, we carried out longitudinal measurements (every two weeks) in which various standard Event-Related Potentials (ERPs) were measured in standard tasks. These measurements were made in the period during which the patients participated in an Early Intensive Neurorehabilitation Programme (EINP). Secondly, we attempted to relate characteristics of the ERPs collected during the first measurement after admission to the EINP to each individual patient's behavioural outcome at the very end of the treatment. Thus, we attempted to assess the predictive value of the different ERP components.

The present study reports on the P300 component of the ERP in a standard oddball task. The P300 is a large, broad, positive potential with a typical peak latency between 300 and 400 ms after stimuli in any modality (Sutton et al., 1965). The most common task for eliciting the P300 is the oddball task, in which low-frequency target stimuli (oddballs) are embedded in a series of nontarget stimuli (standards). The subjects are either required to actively respond to each target, or to count the target stimuli (active condition), or to passively attend to the train of stimuli (this is often used in animal studies or in non-responsive human patients). The P300 usually has a central-parietal scalp distribution, although this depends much on the exact nature of the task. When novel or highly deviant stimuli are used as oddballs, the scalp distribution is more frontal than central-parietal, and the potential peaks a little earlier.

It is then labelled P3a, or novelty-P3 (Courchesne et al., 1975), as opposed to the more classical P300, or P3b, which is the focus of the current study.

The presence of a P300 has been found to be of some predictive value for neurological outcome at the early stages of coma. For instance, 80-100% of comatose patients, traumatic and nontraumatic, who exhibited a P300 regained consciousness (e.g., Gott et al., 1991; Guérit et al, 1999; Kane et al., 2000). No conclusions on the prognosis can be drawn for the absence of a P300, however, because patients without a P300 have been found to have good or bad outcomes alike. In other words, using the presence of the P300 in the early stages of coma as a predictive tool for final outcome is a test with high sensitivity but low specificity. Later after the injury, the P300 has been found to occur in patients in the vegetative (Guérit, 2005; Guérit et al., 1999; Kotchoubey et al., 2001; Kotchoubey et al., 2005), and in the minimally conscious state (Kotchoubey et al., 2005, Laureys et al., 2004b). To our knowledge, there are no longitudinal studies in which P300 amplitude and latency have been related to different levels of consciousness within the same patients.

We thus attempted to correlate P300 amplitude and latency with level of consciousness during the recovery from the vegetative state, and to assess the predictive value of outcome based on the first P300 measurement. Because non-responsive patients are thought not to be able to follow the instructions to count or respond to the oddball stimuli, usually passive oddball tasks are used in which the patients are not given any instruction to pay attention. In healthy subjects, the P300 is usually present under a passive condition to the same extent as in an active condition (Polich, 1989; Rappaport et al., 1991). Guérit (2005) showed some differences between active and passive conditions in some cases of prolonged vegetative state. In at least one case a positive component appeared in the active condition, which was consistently absent in the passive condition. We therefore included both active and passive conditions to elicit the P300 in our measurements.

The study of Guérit et al. (1999) did not only address oddball effects on the P300 in the acute phase, but also observed a processing negativity that appeared at a latency of 300-400 ms with a frontal preponderance. The negativity, which we shall refer to here as the N350, predicted good outcome in 75% of the cases. Guérit et al. (1999) also noted its similarity to a negativity that is frequently observed in sleep onset (e.g., Harsch et al., 1994), although it is a matter of debate whether these negativities reflect the same underlying processes. Anyhow, we shall examine the longitudinal measures for effects on the P300 as well as on the N350.

Methods

Participants

Ten patients with severe brain injury, who participated in an 'Early Intensive Neurorehabilitation Programme' (Eilander et al., 2005b) between November 2002 and January

2004, were included in the study (7 male). Age at the time of injury ranged from 8 to 25 years (M = 17.3 years; SD = 4.4). Time since injury at admission ranged from 6.2 to 19.4 weeks (M = 11.6 weeks; SD = 3.6). All but two patients suffered from traumatic brain injury caused by traffic accidents. Patients participated in the programme between 1.5 to 5.2 months (M = 3.5 months; SD = 1.03). See Appendix 7 for a detailed description of the patients participating in this study: patient 17, and patient 20 to 28.

A healthy control group consisted of 13 persons (7 male); the groups were matched for mean age ($t(21) = 0.16$, $p = 0.876$). All patients and the healthy control group participated in this study following informed consent given by one of the parents, a legal representation or partner (all the patients and the healthy control group aged < 16 years), or by themselves (healthy control group aged ≥ 16). The study has been approved by a medical ethics committee (METTOP).

Observation scales

To assess the Level of Consciousness (LoC) a categorisation was used based on the definitions described by the 'International Working Party Report on the Vegetative State' (Andrews, 1996) and the Aspen Neurobehavioural Conference (Giacino et al., 1997). The categorisation system describes a comatose state, three vegetative sub-states, three non-vegetative sub-states, and a conscious state (see Appendix 3 for the classification scheme in detail).

This classification scale showed high reliability and validity (Eilander et al., 2005a). The inter rater reliability (Spearman's rho) varies between 0.85 and 0.94. The inter-rater agreement (Cohen's weighted Kappa) varies between 0.90 and 0.95. The intra-rater reliability is 0.96 and the intra-rater agreement is 0.94. Correlation of the scores of the rated scores with the Western Neuro Sensory Stimulation Profile (WNSSP, Ansell et al., 1989) varies between 0.85 and 0.90, and with the Disability Rating Scale (DRS) (Rappaport et al., 1982) between 0.88 and 0.94 (Eilander et al., submitted).

Overall LoC at the end of the programme ($LoC_{discharge}$) was determined by the rehabilitation physician, based on Appendix 3, after a discussion with the multidisciplinary treatment team about each patient. Note that the level of consciousness at discharge was measured independently of the ERP measurements, often more than a week thereafter. Thus, the $LoC_{discharge}$ did not necessarily correspond to a particular ERP measurement for a given patient.

To determine the long-term functional outcome, the DRS (Rappaport et al., 1982) as well as the GOSE (Wilson et al., 1998) were administered. The DRS consists of eight items, which can be summed up to values from 0 to 29. A high score on an item indicates a low level of functioning on that aspect. To make the two scales more comparable, the DRS was reduced to 8 categories according to Rappaport et al. (1982): 1=dead (score 30), 2=vegetative state (score 22-29), 3=extremely severe disabled (score 17-21), 4=severely disabled (score 12-16),

5=moderately severe disabled (score 7-11), 6=moderately disabled (score 4-6), 7=mildly to partially disabled (score 1-3), and 8=no disability (score 0).

The GOSE is a one-item rating scale including eight outcome categories and can be administered through a structured interview (Wilson et al., 1998). Outcome categories are: 1=dead, 2=vegetative state, 3=lower severely disabled, 4=upper severely disabled, 5=lower moderately disabled, 6=upper moderately disabled, 7=lower good recovery, 8=upper good recovery.

Data acquisition and analysis

The stimuli were 375 pure tones of 1000 Hz (80%, standard) and 2000 Hz (20%, deviant), with an intensity of 70 dB SPL and duration of 75 ms (rise- and fall time 10 ms). The tones were delivered binaurally through insert earphones. A random inter stimulus interval of 1000 to 2000 ms was used (steps of 1 ms; rectangular distribution). Brain activity was recorded using actively shielded pin-electrodes, by means of the ActiveTwo System (BioSemi, The Netherlands) at a sampling rate of 2 kHz. The total equipment was approved on safety by a Metron QA-90 Safety tester in the Tweesteden Hospital (The Netherlands). The electrodes were placed by using a head cap and electrode gel (Parker Signa) according to the 10/20 system, at F3, Fz, F4, C3, Cz, C4, Pz, and Oz. Linked mastoids served as a reference, which was calculated off-line. Horizontal EOG was recorded from two electrodes placed at the outer canthi of both eyes. Vertical EOG was recorded from infraorbital and supraorbital regions of the two eyes, perpendicular to the pupil. EEG signals were band-pass filtered off-line (0.15 – 30 Hz, 48 dB/octave). EOG artefacts were corrected by means of a linear regression procedure (Gratton et al., 1983). The raw data were segmented into 375 epochs, including a 100-ms prestimulus baseline. Epochs with an amplitude change exceeding ± 200 μV at any channel were automatically rejected. ERPs were averaged separately for the standard and deviant tones.

Peak amplitudes in the individual subject's averaged waveforms were scored at the electrode positions Fz and Pz, as the maximum negative or positive value, respectively, in a window of 200-1000 ms post-stimulus for both the standard and deviant tones. Peak latency was scored as the time at which this maximum occurred.

Procedure

Nine days after a patient was admitted to the treatment programme the first measurements took place. Patients were examined while they were lying in a bed in a quiet room with a constant temperature (23 ± 1 °C). Every two weeks the two oddball tasks were performed at the same time of the day (between 10:30 a.m. and 11:30 a.m). The oddball tasks, which lasted about 10 minutes each, were always performed in the same order: first the passive, and then the active task. The passive task was presented without any warning. After the passive task, the Dutch equivalent of the following instruction was given to introduce the

active task: *'Pay attention! First we are going to explain what you have to do. You are going to hear a lot of beeps, high beeps and low beeps. Pay attention to the high beeps!'*

Every two weeks the rehabilitation physician determined the LoC based on the categories described in table 2. These assessments were performed until the patient was discharged from the programme. The programme was ended when a) a patient was qualified for regular rehabilitation because of recovery of consciousness and cognitive abilities, or b) a patient did not show any recovery in a period of at least six weeks during the programme. These different recovery courses lead to a variation in time span of the patients' participation in the experiment and in the number of measurements.

Long-term outcome was determined by the DRS and GOSE scores at least 2 years after the injury (M = 2.6, SD = 0.28, see the table in Appendix 7 for the exact time intervals). A rehabilitation physician performed the interviews by telephone with a close relative of the patients (partner or parent).

The healthy control group was measured once, in the same position and location, at different times of the day.

Results

Behavioural indices of recovery

At admission, the patients' average LoC score was reflexive vegetative (M = 3.6, SD = 0.52, range 3-5). The average LoC score increased to the inconsistent minimally conscious state (M = 5.9, SD = 1.9, range 3-8) at discharge. Five patients reached a conscious level (LoC 7 or 8), 2 patients were still in the MCS (LoC 5 or 6), and 3 patients were still in the VS (LoC 2-4) at the end of the programme. Overall, these data indicate that during the programme the patient group improved on the mean level of consciousness. However, the level of consciousness at discharge of the programme could not be predicted based on the level of consciousness at the start of the programme. A regression analysis resulted in an equation of $Loc_{discharge}$ = 5.829 + 0.073 * $LoC_{initial}$ (R = 0.026, R^2 = 0.001, Adjusted R^2 = -1,24, $F(1,8)$ = 0.005, p = 0.944).

The long-term outcome scores on the DRS and GOSE could be obtained for 9 patients. Two to three years after the injury the mean score on the DRS was 'severely disabled' (M = 4.4, SD = 2.0, range 1-7), and the mean score on the GOSE was 'low level severely disabled' (M = 3.1, SD = 1.3, 1-6).

Neurophysiological data

In the healthy control group, two participants were discarded because their data contained too many artefacts. A total of fifty recordings were performed in the patient group. Recordings were sometimes plagued by excessive noise, movements, or general resistance on

the part of the patients. The resulting number of measurement that could be successfully analysed was 47 for passive oddball task, and 45 for the active task. In most of the patient data, the peaks and latencies in the individual averages for each measurement were difficult, if not impossible to score. Therefore, following Guérit et al. (1999), we chose not to describe these data by presenting formal statistical tests on unreliable scores of amplitudes and latencies, but to present overall averages as well as individual patient's data, and to describe the findings to the best of our abilities. The patient group was split up into patients that recovered (that is, reached a LoC score of 7 or 8 at discharge, N=5), and patients that did not recover (LoC scores 2-6; vegetative and minimally conscious states, N=5). Grand averages of these two groups are exhibited in Figure 1, along with the averaged waveforms of the healthy control group.

The healthy control group (left panels in Figure 1) showed a classical P300. Statistical comparison of the peak amplitudes at the Fz, Cz, and Pz electrodes confirmed the impression obtained from Figure 1 that its amplitude was maximal at the Pz electrode and minimal at the Fz electrode ($F(2,7) = 8.09$, $p = 0.015$). The normal controls also showed the classical oddball effects in which deviant tones elicited greater amplitudes relative to standard tones ($F(1,8) = 17.63$, $p = 0.003$). The active and passive versions of the oddball task did not result in a statistically distinguishable difference in P300 amplitude ($F(1,8) = 0.27$, $p = 0.617$). Taken together, these data indicate the success of the task manipulation and measurement procedures in normal healthy subjects, because the effects are just as expected based on the vast amount of literature about this task and this brain potential.

Quite a different picture emerged in the patients. First of all, the potentials were a lot smaller in the patients than in the controls. In Figure 1 we used different Y-axis scales for patients and controls to show the data clearly. However, a close look at the Y-axis values reveals that, for instance, the first negative potential (N100) was more than twice the size in the controls than in the patients. Secondly, the patients who did not recover to consciousness (right panels in Figure 1) did not show any appreciable potential after the onset of the tones. There seemed to be some sign of a broad positivity, especially at the frontal electrode in the passive task, but there did not seem to be any oddball effect. In addition, the data looked quite noisy in the patients who did not recover compared to the patients who did recover. Yet the groups were of equal size (N=5) and the total number of measurements for the patients that did not recover was greater (27) than for those that did recover (22).

For the patients that recovered to consciousness, Figure 1 (middle panels) shows a distinct pattern of results. On average, they exhibited a typical P300 to the oddballs, but about 300 ms later than normal – around 650-700 ms post-stimulus – and clearer in the passive task than in the active task. The maximum of the P300 seemed to be central (Cz), rather than the more typical parietal (Pz) maximum. The P300 was preceded by a large negative potential peaking around 400 ms, the N350, with a maximum at the frontal electrode (Fz). The N350 also seemed more prominent in the passive relative to the active task, but did not seem to exhibit an oddball effect.

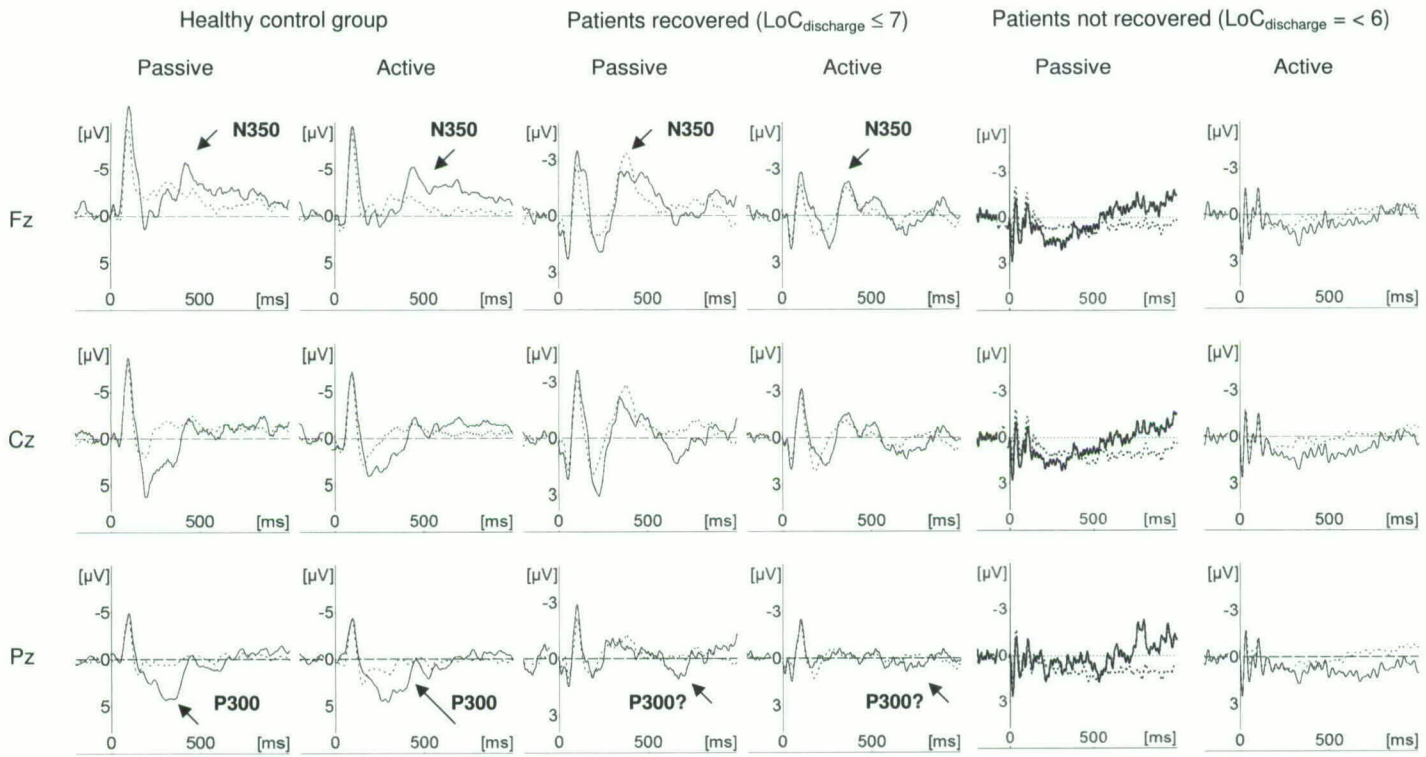


Figure 1 Grand average ERPs in the oddball task, separately for the active and passive tasks, and separately for patients who recovered to consciousness (LoC 7-8) , patients who did not recover (LoC 2-6) and normal controls. Each column consists, from top to bottom, of the electrode positions Fz, Cz, and Pz. Note the different Y-axis scales for patients and normal controls.

In sum, patients showed smaller P300 amplitudes than normal controls. Patients who recovered, but not patients who did not recover showed a small P300, most prominently in the passive task. The most noticeable finding, however, was that patients who recovered showed a large frontal N350, which distinguished them from patients that did not recover. We shall now turn to the question of how consistent these findings were in different patients, and across the different measurements within each patient.

Examples of single measurements. Figure 2 shows some examples of averages based on single measurements for some of the patients and controls. We selected the particular patients with the intent of showing examples of very clear instances of the potentials, very unclear instances, and something in between. We thus tried to convey an impression of the variability that was present in the measurements. The Cz electrode was not displayed in this figure because the most important effects are present on the Fz and Pz electrode, and leaving out an electrode allowed us to present the data more concisely. Figure 2a shows some examples of healthy control subjects. The P300 was present in all participants, although its size varied considerably across subjects. The N350 was hardly discernible in these data, and could not be distinguished from the N200, a similar potential that often precedes the P300 (e.g., Squires et al., 1976). The clearest instance of the N350 was found in the participants displayed in the third column from the left in Figure 2a (active task), but it seemed to be to greater in standards than in deviants.

Some examples of measurements in the patients who recovered are shown in Figure 2b. In these figures, the P300s at the Pz electrode were difficult to locate, especially at the latency of about 700 ms, where the grand average showed the clearest P300. These data of single measurements show that the P300 in the patients was not small because its latency varied much across patients. If that were the case, large individual P300s would have been found at various latencies, which would become 'spread out' in the grand average. It is of course entirely possible that the P300 was small in the patients because of large variability in the single trials, but we had no way of determining single trial latency in this group of patients. The N350 was quite prominent in the patients who recovered, although not in all measurements, as is shown in the 2nd (passive) and 4th column (active task) of Figure 2b. The figure also shows a small (1st column) and large (3rd column) oddball effect on the N350.

As noted above, the data of the patients that did not recover are quite difficult to evaluate. In the average, there were no clearly discernible potentials, but Figure 2c shows some instances of potentials that might be interpreted as N350 or P300, although with less confidence than in the patients that did recover to consciousness.

In sum, the data from the individual measurements displayed in Figure 2 suggest that, although on average a clear pattern of results was present in the waveforms, there was much individual variation across patients and measurements.

***Figure* 2(a)**. Some representative examples of averaged waveforms in the healthy control group

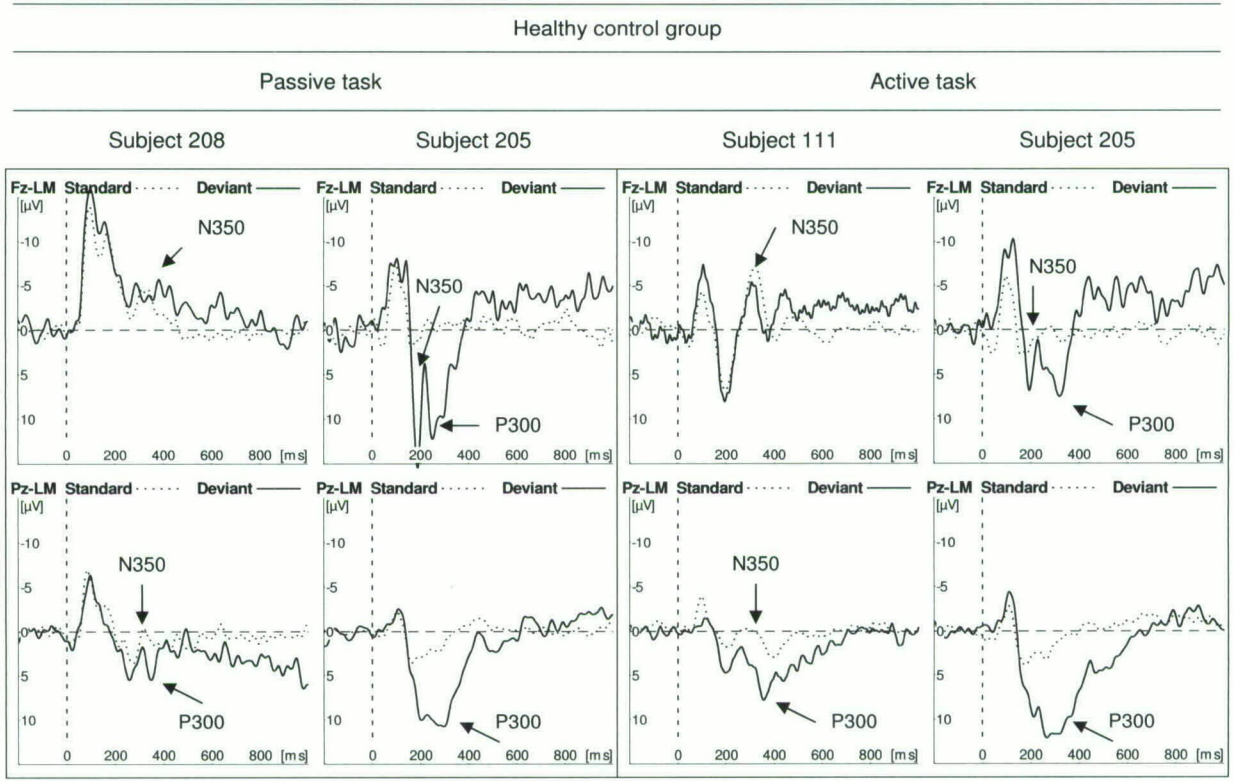


***Figure* 2(b).** Some representative examples of averaged waveforms of single measurement (M = measurement number) in patients who recovered to consciousness

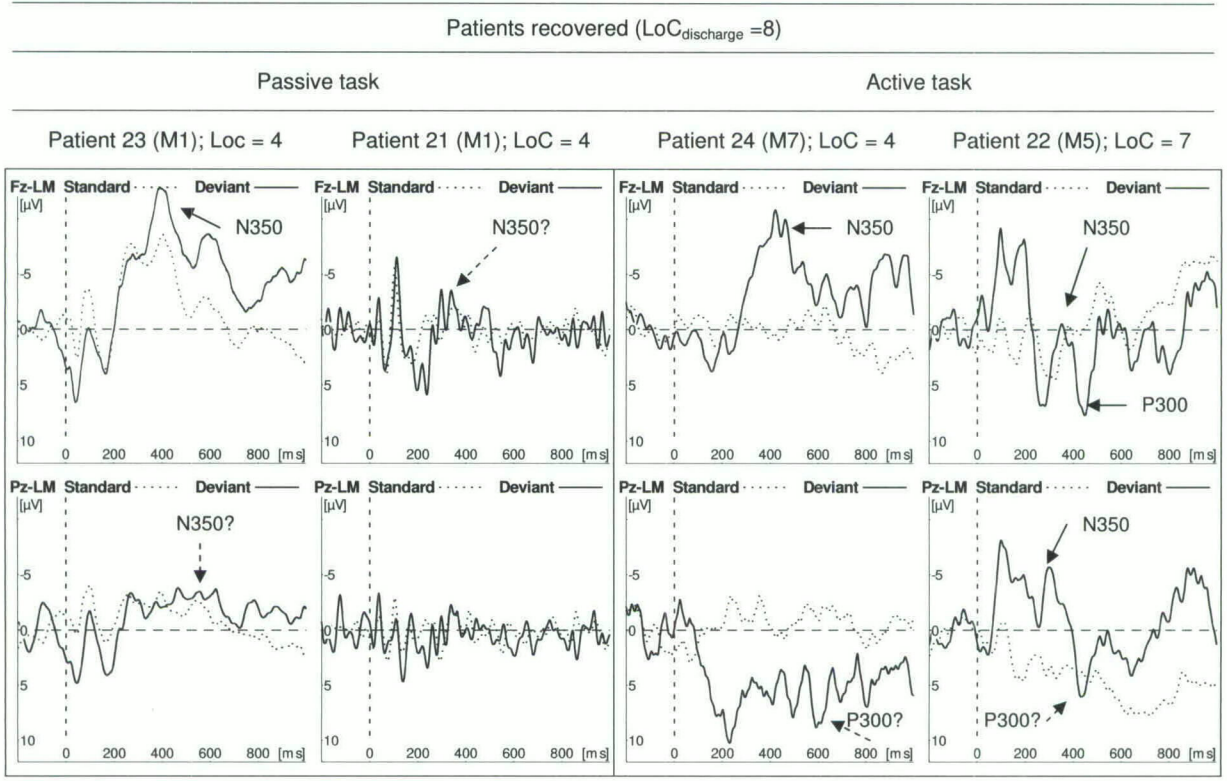
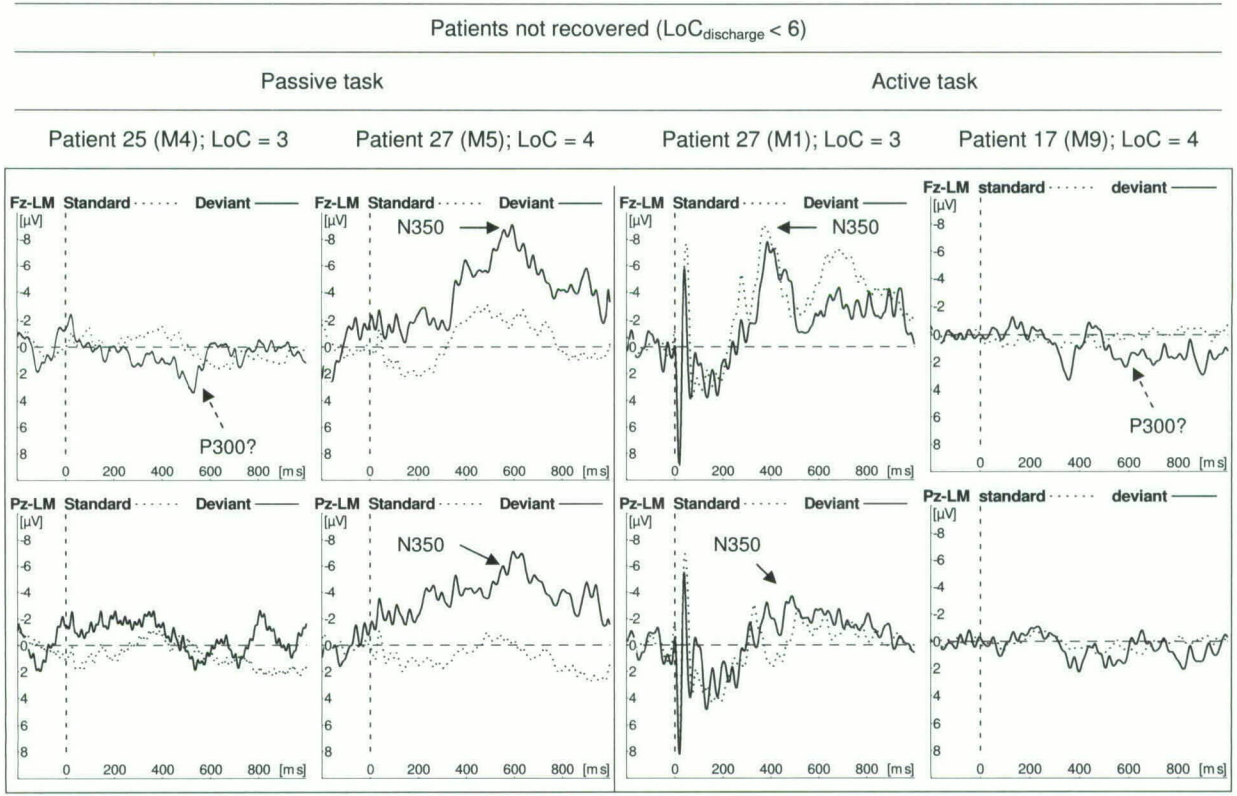


***Figure* 2(c).** Some representative examples of averaged waveforms of single measurement (M = measurement number) in patients who did not recover to consciousness



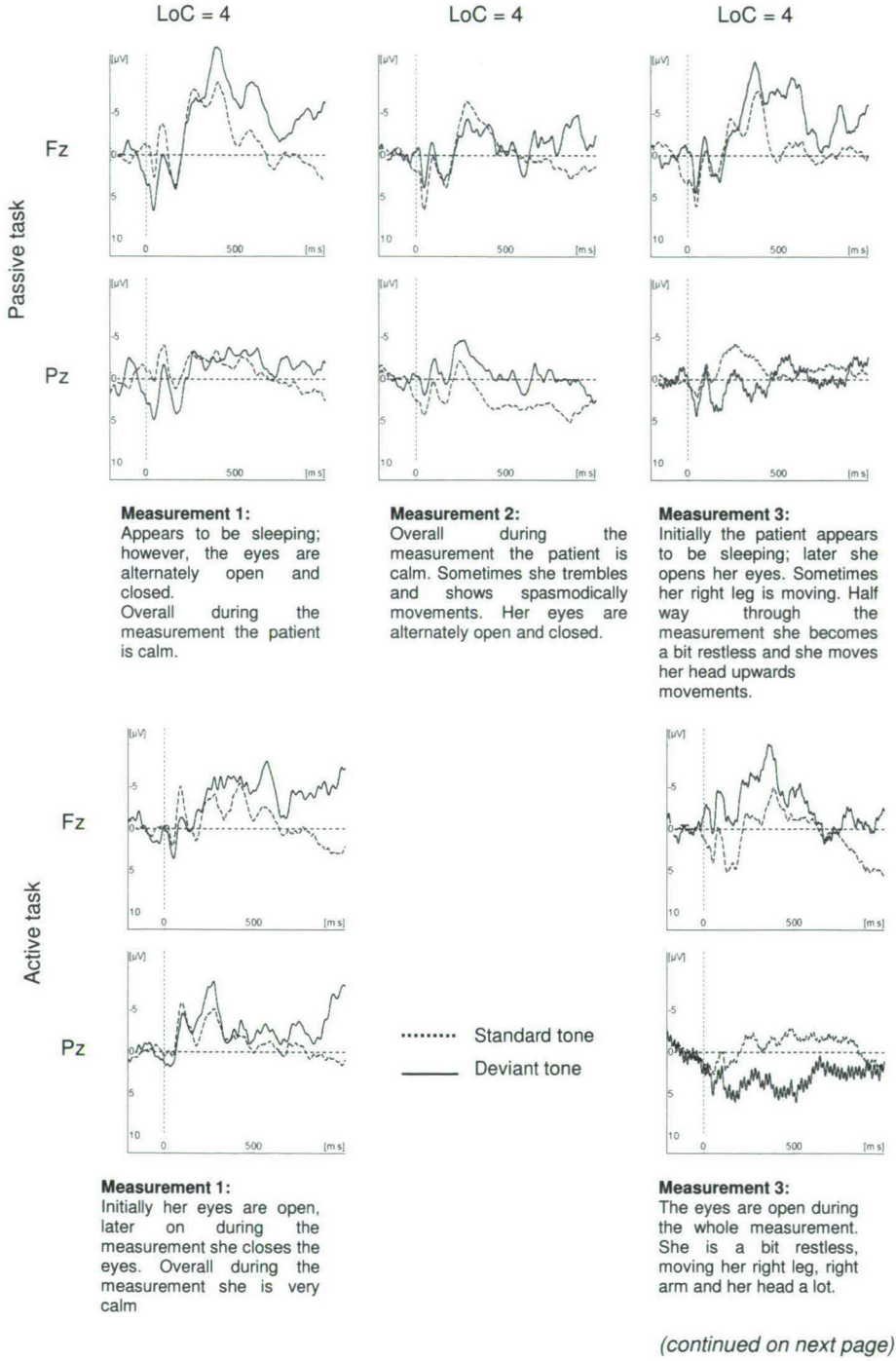
Longitudinal measurements. Figure 3 presents the data from another perspective. Given that an individual patient showed the N350 and the P300, do these phenomena consistently show up in all the measurements of the same patient? Figure 3 shows that this is not necessarily the case, because the patient in question (patient number 26 – see Appendix 7) shows large fluctuations in the amplitude of the N350 and of the P300. For instance, the patient displayed in this figure showed a large N350 in the first measurement when she had a LoC of 4, but the N350 was virtually absent on the seventh measurement when she had a LoC of 7. The same holds for the P300, although a bit less clearly. The P300 was clearly visible in the sixth measurement (LoC 6), but nearly absent in the seventh measurement (LoC 7).

The individual measurements displayed in Figure 3 were marked by descriptions of the arousal state of the patient in the respective measurement. This was done to investigate whether the appearance of N350 was restricted to those measurements in which the patient was sleeping. However, that did not seem to be the case, as can be seen in the patient shown in Figure 3, and we did not find any relation in other patients either. In Figure 3 it can be seem that sometimes a large N350 occurred while the patient was sleeping (measurement 1), sometimes when she was awake (measurement 5). Conversely, sometimes the N350 was not present when she was awake (e.g., measurement 7), but sometimes it was small or absent when she was sleeping (measurements 4 and 8).

All in all it seems safe to conclude that there was no evidence that the amplitude of the N350 or of the P300 consistently increased or decreased as a function of the level of consciousness.

Percentage of occurrence. Another way of looking at the data is to count the occurrence of the N350 and the P300 in each measurement, relative to the total number of measurements (Guérit et al., 1999). We did not count the number of measurements in which the potentials were absent or doubtful, as in Guérit et al. (1999), because those data were too unreliable. Only the measurements in which we could clearly identify the N350 and the P300 were counted. The proportions of the patients participating in this study are displayed in Table 1, separately for the passive and active tasks, and for patients who recovered and who did not. The table shows that for patients who recovered, the percentage of occurrence of the N350 was quite high, both in the active and in the passive task. In the patients that did not recover to consciousness, these percentages were much lower. The P300 had an overall probability of occurrence in both tasks.

Figure 3 Tracking the recovery process of patient 26



Measurement 1:
Appears to be sleeping; however, the eyes are alternately open and closed.
Overall during the measurement the patient is calm.

Measurement 2:
Overall during the measurement the patient is calm. Sometimes she trembles and shows spasmodically movements. Her eyes are alternately open and closed.

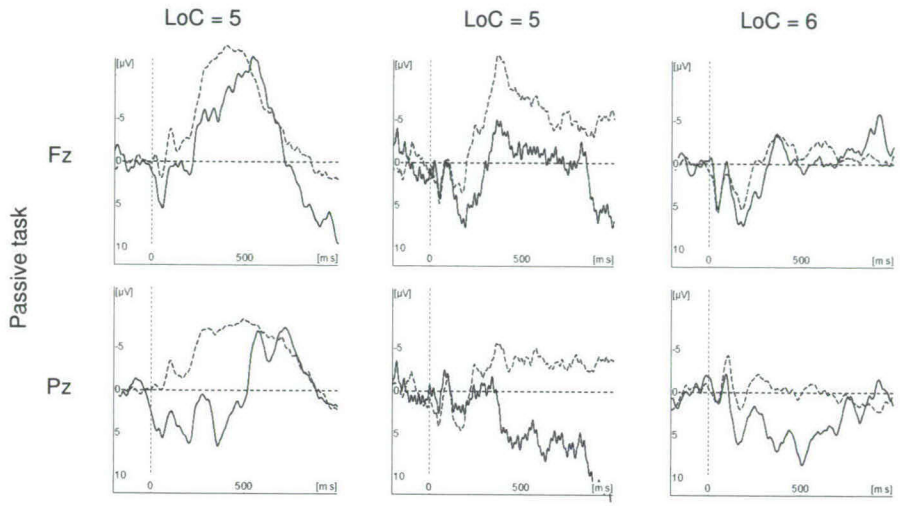
Measurement 3:
Initially the patient appears to be sleeping; later she opens her eyes. Sometimes her right leg is moving. Half way through the measurement she becomes a bit restless and she moves her head upwards movements.

Measurement 1:
Initially her eyes are open, later on during the measurement she closes the eyes. Overall during the measurement she is very calm

Measurement 3:
The eyes are open during the whole measurement. She is a bit restless, moving her right leg, right arm and her head a lot.

(continued on next page)

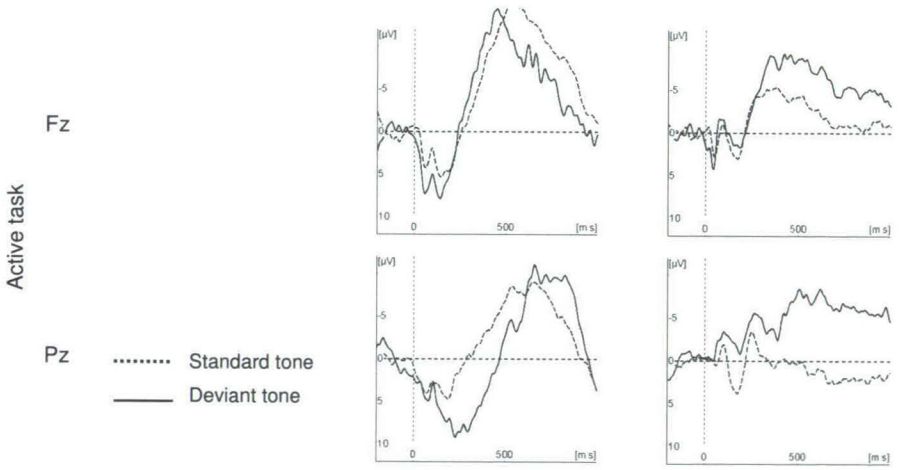
Figure 3 *(continued)*



Measurement 4:
The eyes are alternately open and closed. The patient is overall calm; however, sometimes she moves her head upwards

Measurement 5:
The first part the eyes are closed, a later part the eyes are open. Later on the patient sometimes moves her right leg

Measurement 6:
Initially the eyes are closed, she later opens them, yet is very calm. Later on she starts to become somewhat restless, making movements

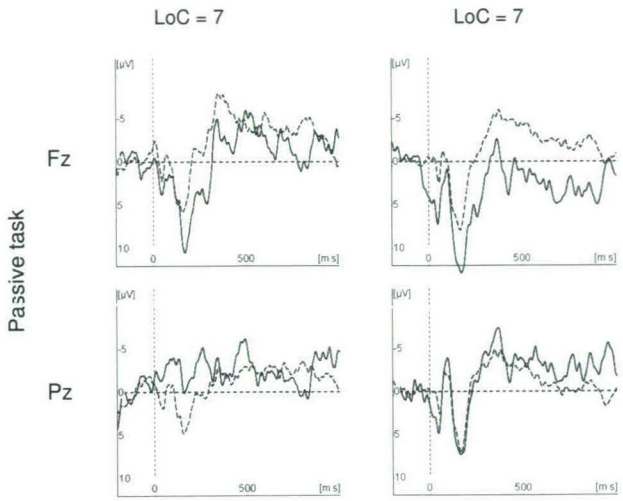


Measurement 5:
The eyes are open during the whole measurement. She is a bit restless, moving her right leg, right arm and her head a lot.

Measurement 6:
The eyes are alternately open and closed. The patient is very calm during the whole measurement

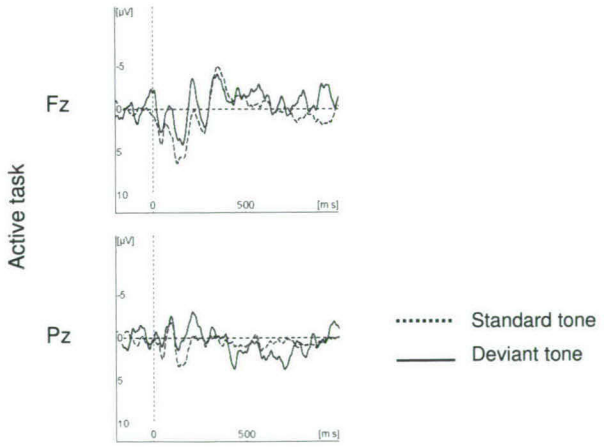
(continued on next page)

***Figure 3** (continued)*



Measurement 7:
The eyes are alternately open and closed. Initially she is calm, later during the measurement she starts to wail a bit, and to cough and to scratch herself

Measurement 8:
Initially she appears to be sleeping, she is relaxed and calm. Later on during the measurement she starts to become restless, trying to grab the earplugs. She sometimes shows some spastic movements of the mouth area



Measurement 7:
The eyes are alternately open and closed. The patient is very calm during the whole measurement

Table 1. Percentage of occurrence of the N350 and the P300, separately for passive and active tasks, and for patients that did or did not recover to consciousness.

	N350		P300	
	Passive	Active	Passive	Active
Recovered	86.4%	68.2%	45.5%	0.09%
Not recovered	11.1%	29.6%	0.07%	0.19%

These data can be taken to mean that, if the N350 is present in a patient, then this patient has a high probability of recovering to consciousness. Conversely, if the N350 is absent, then it is more likely that the patient does not recover to consciousness. For the P300 such predictions were impossible to make. Note, however, that the percentages listed in Table 1 represent aggregates over various measurements and patients, and that it is difficult to make predictions based on single measurements in individual patients.

Another detail that becomes apparent from Table 1 is the notion that the passive oddball task seems to elicit the N350 and the P300 more frequently than the active oddball task, at least in the patients that recovered to consciousness.

Discussion

Event related potentials were examined in severely brain injured patients during their recovery from the vegetative state to consciousness, and compared to healthy controls. We wanted to determine whether the ERP components N350 and P300 exhibited longitudinal changes corresponding to the behavioural indices of recovery, and whether these potentials could be useful in predicting recovery based on an initial measurement. However, it turned out that the amplitudes and latencies of these ERP components were often difficult, if not impossible to score. Therefore, we were unable to analyse the data statistically, and resorted to a description of the averaged data as well as the data of individual patients and measurements as reliably as possible.

As expected for an auditory oddball task, normal healthy controls showed a classical P300 potential, which was greater after deviants compared to standards. The potential had a parietal maximum and frontal minimum, which is also in line with numerous findings in the P300 literature (e.g., Sutton et al. 1965). These findings, which could be statistically confirmed, indicate that the task manipulation and the recording procedures for collecting the brain potentials were successful.

The patient data were not that easy to interpret. We divided the patient group into two equally sized subgroups that differed in final outcome at the end of the treatment ($LoC_{discharge}$ 7-8 versus $LoC_{discharge}$ 2-5; there appeared to be no patient with a $LoC_{discharge}$ of 6), and somewhat arbitrarily referred to these groups as 'recovered' and 'not recovered', respectively. In the patients who did not recover almost no consistent potentials were found. In the group that recovered consistent potentials were indeed found, albeit of much smaller amplitude than in the normal controls. The P300 potential showed the classical oddball effect, but it was much delayed compared to the controls, and its scalp distribution was slightly more central. The delay of about 300 ms seemed to be caused by the presence of a large frontal negativity that preceded the P300, which we termed N350 following Harsch et al. (1994). We used the 'polarity and latency' convention to denote the ERP components (e.g., Donchin et al., 1978), which would seem to imply that the 'N350' follows the 'P300'. However, the N350 preceded the P300 in all instances. We continued using the conventional labels to refer to the theoretically defined ERP components N350 and P300 that observationally appeared (in the patients who recovered) at latencies of approximately 400 ms and 650-700 ms, respectively.

The presence of the P300 in comatose patients has already been demonstrated in patients who were vegetative or minimally conscious for prolonged periods of time (Kotchoubey et al., 2001; Kotchoubey et al., 2005; Laureys et al., 2004b; Menon et al., 1998). Because these studies did not have a longitudinal design, it was not mentioned whether these patients eventually recovered to consciousness. The present data extend those findings in that we found the potentials to appear only in the patients that eventually recovered to consciousness. The same seems to be true for the N350. Guérit et al. (1999) showed that this potential frequently appears in comatose patients in the acute phase, and the present findings suggest that its occurrence is limited to the patients who eventually recover to consciousness. This seems to suggest that the presence of the N350 and the P300 can be of predictive value. However, when we counted the frequency of occurrence of the N350 and P300 in individual measurements, only the N350 seemed to have some predictive value. It occurred more frequently, but not always, in patients who recovered relative to patients that did not recover. We take these findings to mean that the presence of the N350 might indicate favourable outcome, but that its absence does not necessarily imply bad outcome. Similar conclusions have also been drawn for the P300 component of the ERP (Guérit et al., 1999).

An interesting question concerns the functional significance of the N350. Nielsen-Bohlman et al. (1991) discussed the possibility that the N350 is functionally related to the mismatch negativity (MMN). Guérit et al. (1991) dismissed that possibility, mainly based on the argument that its latency surpasses that of the MMN in the same patients. The present data also speak against a functional relationship between the N350 and the MMN. First, in our data the deviant stimuli did not consistently evoke a greater N350 than standard stimuli. Secondly, we have investigated the MMN in the same patients (Wijnen et al., 2007), and not was its latency shorter than that of the N350, but the recovery patterns of the MMN and the N350 were

also different. The MMN remained small until LoC 5, after which a sharp sudden increase was found when the patients progressed to LoC 6. No such sudden increase occurred in the present data for the N350. Taken together, the available evidence does not seem to suggest any functional relationship of the N350 and the MMN.

The N350 has been most frequently associated with sleep, in particular with Stage 2 sleep (e.g., Harsch et al., 1994; Nielsen-Bohlman et al., 1991). It is therefore possible that the N350 occurred in the patients of the present study because they were asleep during the measurement. Although we cannot rule out this possibility completely because we did not formally analyze the sleep stages based on EEG measurements for these patients, we also think that this is unlikely. Behavioural observation of the patients indicated no relationship between sleep and the occurrence of the N350. Figure 3 showed some examples of the N350 recorded during both sleep and waking. Furthermore, the patients who did not recover to consciousness were also sometimes asleep and sometimes awake during the measurements, and never showed a N350. We acknowledge that the latter argument is not unreservedly convincing because we never recorded any ERP component in those patients, and that the first argument may be countered by noting that the patients may have been asleep for a part of the measurement, and that the average reflects the whole measurement. To elucidate the issue further, the background EEG could be analysed and separate ERP averages could be made for periods with and without Stage 2 sleep.

Our findings on the longitudinal changes of the N350 and the P300 were reasonably clear; we did not find evidence for consistent changes with recovery to consciousness. The amplitude of both the N350 and the P300 did not consistently change as a function of the level of consciousness. The patient discussed in the Results section was a clear example of this notion; she showed large amplitudes of the N350 and the P300 in the initial measurements, and they decreased in later measurement, but sometimes also increased again, without a seeming relationship with the level of consciousness.

A final remark should be made about the difference between the passive and the active oddball tasks. Guérit (2005) found that the active task sometimes elicits greater potentials than the passive task, but we were unable to replicate that finding. To the extent that there were differences between the two versions of the tasks, the passive task showed greater amplitudes relative to the active task. Furthermore, counting the occurrence of the potentials suggested that they both occurred more frequently in the passive compared to the active task. It is possible that the active oddball task elicits greater amplitudes when the patients have recovered to a stage in which they are able to 'consciously' classify the standard and deviant stimuli, and that there was no such patient included in the present study. The overall outcome of the present group was not very favourable. It is also possible that effects of task were confounded with time-on-task. The active task necessarily followed the passive task on each occasion, and these tasks were presented after various other tasks had already been administered (see the other chapters). Thus, perhaps by the time the active task was administered, the patients were too tired and

their processing resources for the classification task were exhausted. This issue clearly warrants further investigation, because when consistent differences between active and passive versions of the oddball task can be demonstrated in individual patients, this might be a sign that they understood the task instructions.

In sum, the present study replicated earlier findings that N350 and P300 can be measured in comatose patients, and extended those findings to the post-acute phase, during the recovery from the vegetative state to consciousness. Although no evidence was found that the N350 and the P300 changed as a function of recovery, we did find some evidence that outcome can be predicted from the presence of the N350. These findings are important because predicting outcome after severe brain injury is not possible based on behavioural indices alone.

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Chapter 7

General Discussion

The primary goal of this thesis was to investigate the relationship between behavioural and electrophysiological indices of consciousness, during the recovery from the vegetative state to consciousness. To this end, an extensive longitudinal study was undertaken, in which a group of vegetative patients underwent fortnightly measurements during the treatment programme intended to facilitate their recovery from the vegetative state to consciousness (the Early Intensive Neurorehabilitation programme (EINP). The measurements consisted of various tasks during which different electrophysiological measures were taken, intended to probe and measure a range of cognitive and neurophysiological mechanisms. Two rather broad research questions were formulated, bearing on the longitudinal changes in neurophysiological reactivity during the recovery process, and on the feasibility to predict the final outcome of the recovery process based on the electrophysiological measurements at the start of the treatment programme. These two research questions will now be addressed separately.

Longitudinal changes in neurophysiological reactivity

The patients' level of consciousness was measured using the PALOC-s described in Appendix 3 of this thesis. This scale was based on the literature about the terminology and the definitions described by the 'International Working Party Report on the Vegetative State' (Andrews, 1996) and the Aspen Neurobehavioural Conference (Giacino et al., 1997). It is an ordinal scale in which the levels of consciousness are not necessarily equally spaced as in an interval scale. For instance, the difference between LoC 2 (hyporesponsive state) and 3 (reflexive state) might be of an entirely different magnitude than the difference between LoC 4 (high active level) and 5 (transitional state), if only because of the fact that the first difference is within the vegetative state and the second is related to the transition between the vegetative and the minimally conscious states. However, for practical purposes, the scales were treated as interval scales, and plots of the longitudinal changes in LoC were always drawn with equal distances between levels on the X-axis. It should be kept in mind, however, that this procedure was only used to present the data more clearly, and that the clinical reality is one of qualitatively rather than quantitatively different levels.

It is an interesting theoretical question whether the recovery process is slow and gradual, or whether sudden jumps and transitions exist. The behaviourally defined level of consciousness of the patients participating in the present studies increased during the treatment programme, and the increase appeared to be gradual and linear, without clear jumps or transitions (e.g., Chapter 4). However, as explained above, this might be an artificial effect due to plotting levels with equal distances. Anyhow, an important question in the context of this thesis is whether the electrophysiological measures studied in this thesis were correlated with these behavioural levels. Should they also show a gradual linear increase, then it can be concluded that a good correspondence between the observational and electrophysiological

measures exist. The answer is that it depended on the administered task and on the neurophysiological response system probed by that task.

For instance, a gradual linear increase in autonomic reactivity was found (Chapter 4), but the elementary sensory processing did not show any change at all (Chapter 3). The Mismatch Negativity showed a sudden increase in amplitude with the transition between LoC 5 and LoC 6, and the P300 and N350 recorded in the auditory oddball task showed an inconsistent relation to the consciousness level. This pattern of results is best interpreted within a view of recovery following phylogenetic and ontogenetic development (Cramer and Chopp, 2000; MacLean, 1970; 1978; Teitelbaum, 1974). Development of the central nervous system, and possibly also of cognitive functions, occurs in a bottom-up fashion (Cramer and Chopp, 2000; Kolb and Whishaw, 1990). That is, elementary sensory processing mediated by subcortical (e.g., brainstem) and primary cortical structures develop before more complex ('higher') functions mediated by more complex (association) cortical structures. In the electrophysiological components that were the focus of this thesis, complexity is reflected in the component's latency; the more complex the function, the longer the latency of the associated electrophysiological component. Recovery from the comatose state to consciousness seems to follow a similar pattern; recovery of primary sensory processing seems to occur before the recovery of more complex processes. The following diagram is an attempt to visualize this notion.

	Function	**Associated Brain structures**	**Electro physiological Measures**	**Recovery Pattern**
Bottom	Elementary Sensory processing	Subcortical and primary cortical	Evoked Potentials BAEPs, SSEPs, VEPs	None (already recovered)
	Sensory processing (mismatch detection)	Cortical	Mismatch Negativity	Transition between LoC 5 and 6
	Elementary Cognitive processing	Cortical	N350 P300	Inconsistent
Top	Arousal	Higher cortical Autonomic	Heart rate Skin Conductance	Gradual, linear

Note that this diagram is not an attempt to describe all aspects of cognitive functioning and brain processes studied in this thesis, as the model underlying the diagram will surely run into problems when looked at in detail. It should rather be viewed as a heuristic, a steppingstone for the description of the main findings of this thesis. Note also that the arousal functions, measured in this thesis by heart rate variability and skin conductance level, are placed at the top of the hierarchy. In diagrams such as the above, arousal is often placed at the bottom of processing; as a prerequisite for further cognitive activity. Again, choices in the diagram should not be seen as absolute truths; the diagram only serves as a heuristic that serves to present the present findings concisely. The present choice was motivated by the work of Tranel and Damasio (1994), who found that autonomic arousal can be disrupted by many and diffuse cortical lesions. They view autonomic arousal as the result rather than the cause of higher cognitive process, in which information from the environment from many sources is integrated. The subcortical structures involved in autonomic responses are output structures not input structures as in the elementary sensory processing. If this view is correct, then it is no surprise that the recovery of the arousal system (Chapter 4) resembled the behaviourally observed recovery most closely.

This thesis did not result in clear discrepancies between behaviourally defined levels of consciousness and electrophysiological measures. That is, the recovery of the electrophysiological measures seemed to correspond reasonably to the behaviourally defined pattern of recovery. There is perhaps one exception; the mismatch negativity showed a sharp increase between LoC 5 and LoC 6 (see Chapter 5). This was somewhat unexpected, because an important behavioural transition between the vegetative and the minimally conscious state occurs just before that; between LoC 4 and LoC 5. LoC 5 is a somewhat disputed stage for that matter, and is called the 'transitional state' for good reason (Andrews, 1996). The present results on the MMN suggest that the more important transition occurs between LoC 5 and LoC 6, when the patients start to show inconsistent reactions to the environment and elementary forms of comprehension. It appears that the ability to discriminate sounds, which is what the MMN measures, is a prerequisite for this stage, which makes perfect sense of course.

These findings can be interpreted to suggest that perhaps LoC 5, the transitional state, should be viewed as part of the vegetative state rather than the minimally conscious state. Other than that, there was no clear evidence that the observationally defined stages should be significantly altered, let alone refined.

Predicting outcome

If the final outcome of a particular patient could be reliably predicted, then this would be a great help for clinicians with limited resources to determine which patients to invest those

resources in, and which patients can be referred to a nursing home immediately because no improvement can be expected. This would save a lot of effort, as well as considerable costs for society. Note however, that people are not economical goods, and such considerations quickly run into ethical problems. No matter how strong the predictive value turns out to be, there might always be the famous exception to the rule of a patient with a very bad prognosis who suddenly, quickly, and unexpectedly regains consciousness. Who is able to justify the choice to be made in such cases?

This ethical consideration should, however, not prevent the scientific question to be asked whether prediction of recovery is at all possible. Prediction of final outcome is not possible based on observational scales alone. This is a very clear result of the present thesis, in which regression analyses yielded next to zero predictive value of the behaviourally defined scales. But that was already clear based on the verbal description of the individual patients. Readers who take the trouble to read through the individual cases (Appendix 7) will no doubt be surprised sometimes when a particular patient suffered a terrible injury, had to undergo many surgical procedures associated with many complications. Then, just when the prospects look very bad, such a patient can suddenly start to recover to full consciousness. In sum, little can be said about the final outcome of recovery or treatment based on observation alone.

The electrophysiological measures studied in this thesis were clearly better at predicting final outcome. Various measures collected on the first measurement immediately after entrance to the treatment programme were able to predict final behavioural outcome with varying degrees of success. Even elementary visual processing index by flash VEPs showed some predictive value for outcome. The potentials recorded in the auditory oddball tasks, particularly the N350 in the passive oddball task, predicted outcome quite well. However, the final pattern of results of recovered patients was still very much different from normal healthy subjects. For instance, the amplitudes remained considerably lower in recovered patients relative to controls, and the N350 was hardly present in healthy controls.

The measure that was able to most reliably predict final outcome was the MMN with 100% sensitivity and specificity (see Chapter 5). The MMN had already been shown in the acute phase after the injury to predict which patients would progress to the vegetative state, and which would not (Fischer et al., 2004). Their results can thus be extended to the post-acute phase as well. Patients with a MMN amplitude of 1 μV or more have a good prognosis of showing the sudden transition between Loc 5 and LoC 6, and then progressing to full recovery.

It should be noted that the patient group in which outcome was predicted based on electrophysiological measurements was quite small (about 10 patients). Thus, together with the above ethical considerations, one should be extremely cautious in predicting behavioural outcome and founding clinical decisions based on these findings. However, these findings seem to be a promising area for further research into this important matter.

Concluding remarks

This thesis reports on investigations of electrophysiological measurements in patients in the post-acute phase after severe traumatic injury, during the recovery of the vegetative state to consciousness. Several aspects make this thesis rather unique. First, there is very little research involving electrophysiological measurements in patients with severe traumatic brain injury in the post-acute phase. Most research concerns patients investigated in the acute phase, usually within four to six weeks after the injury. The present thesis complements that research with data collected during later phases of recovery. Secondly, the longitudinal aspect of the present research is special in that there is virtually no database on neurophysiological reactivity during the various stages of recovery. Third, most of the patients in this thesis were adolescents or young adults, which are a group with high risks of traumatic brain injury due to traffic accidents; yet there is very little research available about this group. Taken together, these data provide a unique view of the electrophysiological correlates of recovery from the comatose state in this specific group.

On the downside, the group was quite small. Therefore, conclusions based on this research should be made with caution. The individual variation in the reactivity of the patients and their outcome was quite large. Therefore, when larger patient groups are studied, the final conclusions might be different than based on the limited group that was studied here. The present conclusions were formulated cautiously, and also for this reason, conclusions related to more theoretical questions about consciousness were avoided. Clearly, this research could have great impact on theoretical questions related to consciousness, which perhaps form the core of modern cognitive neuroscience. However, the groups were too small and too atypical to found firm conclusions in this respect. Rather, the thesis was meant to present as much as possible descriptive data on the topic and the patients under study. It presents more like a first step that can be used as a reference for further investigations.

What this thesis clearly does demonstrate is that the topic of electrophysiological measurements made longitudinally, during the recovery from comatose or vegetative states to consciousness, particularly in this patient group, maybe a fruitful area for further investigation, which has the potential to be of great importance for clinicians dealing with such patients, for the patients themselves, and for their relatives.

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Samenvatting (Dutch summary)

In dit proefschrift is het herstelproces in kaart gebracht van kinderen en jongeren die na een ernstig niet aangeboren hersenletsel in een vegetatieve toestand waren. Er is onderzocht hoe veranderingen in gedrag zich verhouden tot veranderingen in neurofysiologische reactiviteit tijdens herstel van een vegetatieve naar een bewuste toestand. Hiertoe zijn observatiemethoden vergeleken met verschillende neurofysiologische reacties. Ook is gekeken naar de verschillen in neurofysiologische reactiviteit tussen patiënten die uiteindelijk herstellen naar een bewuste toestand en patiënten die vegetatief blijven.

In hoofdstuk 3 werden elementaire zintuiglijke reacties onderzocht met behulp van Evoked Potentials. Brainstem Auditory Evoked Potentials (BAEPs) werden gemeten om de verwerking van auditieve prikkels te onderzoeken. Somatosensory Evoked Potentials (SSEPs) werden gemeten om de verwerking van tast prikkels te onderzoeken. Visual Evoked Potentials (VEPs) werden gemeten om de verwerking van visuele prikkels te onderzoeken. BAEPs en vroege componenten van SSEPs en VEPs waren herhaaldelijk aanwezig bij alle patiënten. De EPs veranderden niet tijdens herstel van een vegetatieve naar een bewuste toestand. De primaire verwerking van auditieve, visuele en tast prikkels was actief bij deze patiënten. De patiënten verschilden op de latere componenten van de SSEPs en VEPs. Alleen de patiënten die uiteindelijk herstelden naar een bewust toestand vertoonden deze latere, corticale componenten. Een iIndex van het globaal corticaal functioneren kan worden gebruikt in de post-acute fase voor prognostische doeleinden. Vervolgonderzoek naar EPs in de post-acute fase zou gericht kunnen zijn op VEPs, vanwege zijn voorspellende waarde voor herstel naar een bewuste toestand..

In hoofdstuk 4 werd de reactiviteit van het autonoom zenuwstelsel op zintuiglijke stimulatie onderzocht. Door hartslag en huidgeleiding te meten hebben is inzicht verkregen in het functioneren van de verschillende takken van het autonoom zenuwstel. Sympathische activiteit was hoger en parasympathische activiteit was lager, na een stimulatieperiode. Naarmate de patiënten herstelden naar een bewuste toestand nam de reactiviteit van het sympathische zenuwstelsel *tijdens* de stimulatie sessie, toe, en de reactiviteit van het parasympathische zenuwstelsel af. De veranderingen in de reactiviteit van het autonoom zenuwstelsel waren lineair gerelateerd aan de veranderingen in gedragsaspecten van het herstel. Het blijkt dat zintuiglijke stimulatie bij deze patiënten arousal tot stand brengt. Daarnaast blijkt dat zintuiglijke stimulatie hen steeds meer kan 'arousen' of activeren als er herstel plaats vindt.

In hoofdstuk 5 is de preattentieve informatieverwerking van auditieve prikkels onderzocht met behulp van de Mismatch Negativity (MMN). De amplitude van de MMN nam toe tijdens herstel naar een bewuste toestand. Een opvallende toename werd waargenomen tijdens herstel binnen de subniveaus van de minimaal bewuste toestand. Op gedragsniveau vond op dit moment een belangrijke veranderring plaats in de manier waarop de patiënten communiceerden en handelden. Vanaf dat punt waren de patiënten in staat om opdrachten te verrichten, echter nog wel onregelmatig. De amplitude van de MMN had een grote voorspellende waarde voor herstel naar een bewuste toestand. Alle patiënten die uiteindelijk naar een bewuste toestand herstelden lieten op de eerste meting een grotere MMN zien in vergelijking met de patiënten die niet herstelden. Het opmerken van verschillen tussen externe prikkels blijkt een belangrijke eigenschap voor herstel naar een bewuste toestand. Vervolgonderzoek zou zich kunnen richten op dit verschil tussen prikkels, door te variëren met de deviantie in het MMN-paradigma.

In hoofdstuk 6 werd de attentieve of cognitieve informatieverwerking van auditieve prikkels onderzocht met behulp van de P300. De P300 was niet optimaal in vergelijking met een gezonde controlegroep. Wel waren er verschillen tussen patiënten. De P300 was alleen aanwezig bij patiënten die uiteindelijk herstellen naar een bewuste toestand. De P300 heeft daarom een voorspellende waarde voor herstel naar een bewuste toestand. De P300 veranderde niet met herstel van een vegetatieve naar een

bewuste toestand. Vervolgonderzoek is noodzakelijk om te kijken naar eventuele veranderingen in de P300 tijdens verder herstel. Als patiënten weer in staat zijn om cognitieve gedragstaken uit te voeren, zal de P300 wellicht meer gaan lijken op die van een gezonde controlegroep.

Deze resultaten laten zien dat het herstelpatroon van VS naar bewustzijn afhankelijk is van welk aspect van het herstelproces wordt bestudeerd. Wanneer we gebruik maken van observatiemethoden verloopt het herstelproces gradueel en continue. De metingen van EPs laten zien dat in de huidige patiëntengroep, de primaire informatieverwerking (weer) intact is. Wanneer we het herstelproces onderzoeken vanuit het AZS zien we een lineair en continue patroon. Het herstel van pre-attentieve informatieverwerking, gemeten met behulp van MMN, verloopt echter discreet. Hierin vindt een belangrijke stap in herstel plaats binnen de subniveaus van de minimaal bewuste toestand. De MMN amplitude laat een plotse toename zien, tegelijkertijd met een gedragsverandering op communicatieniveau. Attentieve of cognitieve informatieverwerking, gemeten met behulp van de P300, verandert niet met herstel van VS naar bewustzijn, en is nog niet optimaal wanneer herstel van bewustzijn heeft plaatsgevonden. Herstel van cognitieve functies zal wellicht plaats gaan vinden in een later stadium, waarbij de P300 optimaal zal worden zoals waargenomen in een gezonde normgroep.

Dit proefschrift laat ook zien dat kleine gradaties binnen en tussen VS en MCS belangrijke informatie verschaffen over het herstelproces. De acht subniveaus van de gebruikte observatieschaal (PALOC-s) kunnen worden herkend op gedragsniveau. Ook de neurofysiologische maten laten veranderingen zien op de subniveaus. De verschillende neurofysiologische parameters verhouden zich ieder op een verschillende manier tot gedrag tijdens herstel. Juist de kleine gradaties in de neurofysiologische reactiviteit ontsluieren stappen in herstel die wellicht onopgemerkt zouden zijn wanneer louter gebruik zou worden gemaakt van observatiemethoden. Met name over de scheidingslijn tussen VS en MCS kan worden gespeculeerd.

Ook is in dit proefschrift bewijs gevonden voor de prognostische waarde van neurofyiologische reactiviteit in de post acute fase. Er bestaan verschillen in neurofysiologische reacties tussen VS en tussen MCS patiënten, terwijl op dat moment op basis van observatiemethoden nog geen verschillen te ontdekken zijn tussen de patiënten. Het is belangrijk de neurofysiologische reacties op te merken, aangezien ze herhaaldelijk gerelateerd aan herstel naar een bewuste toestand. Of de gevonden neurofysiologische reacties bewijs zijn voor het bewustzijn en het cognitief verwerken van omgevingsprikkels op het moment van onze metingen, is dan van secundair belang.

Appendices

Appendix 1

The Early Intensive Neurorehabilitation Programme (EINP)

Inclusion criteria of EINP

The Early Intensive Neurorehabilitation programme is focused on children and young adults (aged 0-25) who suffered a severe acquired brain injury. After injury they were in a prolonged vegetative or minimally conscious state. In addition, the following inclusion criteria are applied concerning indication for EINP:

- the patient must be medically stable, i.e:
    - the patient is no longer dependent of equipments concerning the basal body functions
    - the patient no longer needs intravenous food or medication supply
    - the patient does need extra oxygen supply
- in cases of traumatic brain injury the insult may be no longer than six months before admission
- in cases of non-traumatic brain injury, the insult may be no longer than three months before admission

In general, the duration of EINP can take 14 weeks, consisting of a two-week observation period, and 12 weeks of treatment. An evaluation takes place halfway through the treatment. When there is no or minimal progress within this first evaluation period, EINP is finished. In addition, when progress does occur at any time point, an indication for regular, regional rehabilitation is given. EINP is aimed at five main goals:

- optimizing the physical condition
- provoking the abilities for movement
- stimulation of the level of consciousness towards alertness
- get going the communication abilities
- supporting and educating the family, and if possible the patient in acceptance of the (end)condition

Framework of EINP: five main parts

1. Stabilising the basal vegetative functions. Mostly the attention of rehabilitation nurses is focused on
    a. Condition of nutrition: abolishing under nourishment as a consequent of high metabolism
    b. Condition of the skin: abolishing the risk for decubitis and nursing contractures
    c. Condition of the pulmonary dysfunction caused by diminished respiration
    d. Curing or avoiding diverse infections
    e. Removal of technical aids such as a tracheal tube and catheters of blister because of possible appearance of complications
2. Presenting an environment with a structured day rhythm and diverse activities, which together lead to an everyday life pattern. In the environment different people are situated (other patients,

nursing staff, therapists, and family members), in a lively, more or less domestic atmosphere. The patient is involved in this environment as much as possible (preferably mobilized in a wheelchair). Within this setting it is sometimes (or regularly) possible for children and young adults to spend weekends with their family (provided that good care is guaranteed), either the family can visit the rehabilitation centre very often.

3. Diverse paramedical therapies: physical therapy, occupational therapy, and if indicated, speech therapy. Physical therapy is focused at normalising the muscular tone, in such a way that atypical movement patterns and limitations are minimized. In addition, directed motorial reactions are intensively stimulated. Physical therapy takes place every work day, unless indicated otherwise. Occupational therapy (three times a week) is focused at opposing the limitations in arm, and hand functioning, encouraging diverse cognitive processes, encouraging mobility (positioning, standing) and providing interventions for motor disorders (e.g. wheelchair devices, splints, adapted tableware). To all the persons involved with the patient (including the family members) advices are offered on how to handle the patients, so that chances of learning inaccurate movements are limited. Speech therapy (three times a week) involves normalising the sensibility and the oral reflex activity of the mouth area, advise concerning mouth care, and if possible, providing eating and drinking support. In addition, the speech therapy involves the exploration of communicative possibilities.
4. Stimulation programme: the systematic presentation of diverse sensory and/or cognitive stimulation. Every stimulation programme is focused on the individual patient. Whether sensory and/or cognitive stimulation is necessary depends on the level of consciousness of the patient on the given moment.
5. Intensive support of the direct relatives (parents, brothers, sisters, partners). This support involves providing education, professional support during the grieving process, and guidance in the post-treatment trajectory. Prior to the admission of a patient, the family is invited by a social worker to give information and to guide a visit to the rehabilitation centre. After admission a comprehensive conversation takes place with the neuropsychologist with the aim to give some insight to family in the functioning of the brain, the way this function is disturbed, and the way this happened with their family member. In addition, the goals and limitation of the treatment, the time schedules and treatment perspectives are explained (as well in positive as in negative cases). Also, the possibility exist to guide brothers and sisters. Conversations on the treatment progress take place regularly during the treatment programme. Family members are offered to participate the programme as it is offered to the patient. In addition, it is possible to accompany a therapy at least once a week.

Treatment period

Regular admission

A regular admission can be divided into three phases

- *The observation period*: within the first two weeks after admission the paramedical therapies commence, a collective investigation of the patient takes place involving all therapists. The treatment goals are formulated for each discipline, video registration takes place to determine the

initial condition, and the Western Neuro Sensory Stimulation profile is administered. The observation period is ended with an observation discussion in which the treatment goals of the different disciplines are converted into a general treatment design. The rehabilitation physician discusses the treatment design with the family.

- *Treatment period 1*: initially the stimulation programme is started. After six weeks this programme is evaluated, unless earlier evaluation is necessary. In addition, a video recording takes place to determine the clinical condition. After each stimulation moment a report is written on how the patient reacted to the stimulation. To follow the possible progress, the Western Neuro Sensory Stimulation Programme is administered every two weeks. This period is ended with a discussion on the treatment design, for which every therapist makes a report of the given period. The rehabilitation physician discusses the information of this meeting with the family.
- *Treatment period 2:* within this period the stimulation program is progressed comparable to treatment period 1. It is possible that this period is oriented to the follow up trajectory. Again this period is ended with a discussion on the treatment design (end discussion), and end reportage is made by all of the therapists. The situation is recorded on video, to determine the end condition of the patient. At the end of the programme the focus is on a quick transfer to the follow up trajectory.

Observation period

In cases of brain damage caused by anoxia, the treatment period progresses in a different way. The first two weeks after admission exist of an observation period. The six following weeks are spended on treatment. In week nine an end discussion takes place. In week ten the patient is discharged from the RCL to the hospital.

Extended treatment period

The end discussion of both the regular and the observation admissions can lead to the following three follow up trajectories.

- When the patient shows no or minimal progress during the total treatment period, it is decided to end the stimulation programme and to get discharged from the RCL. Application to and support with follow up possibilities will be performed together with the family.
- When at the end of the treatment period or earlier, the patient shows such progress that he or she is indicated for regular rehabilitation, application for follow up treatment will take place.
- When a patient shows progress during the treatment period, but not enough to be indicated for further regular rehabilitation, it is possible to extend the treatment period, possibly with specific treatment goals.

Appendix 2

Glasgow Coma Scale (GCS)

Assessment of coma and impaired consciousness. A practical scale.
Teasdale G, Jennett B (1974)

E	Eye opening	M	Motor function	V	Verbal
		1	None	1	None
1	None	2	Extends to pain	2	Grunts
2	To pain	3	Abnormal flexion to pain	3	Inappropriate words
3	To sound	4	Normal flexion to pain	4	Confused
4	Spontaneously	5	Localises pain	5	Oriented
		6	Normal		

- Choose the best obtainable score, left or right.
- Apply painful stimuli to arms or supraorbitally, not to legs.
- Differentate M = 6 from grasp reflexes by, for example, asking th epatient to open his/her hand too.
- Score M = 5 if, in response to a supraorbital stimulus, the patient raises his/her hand past the chin, or if in response to a nail-bed stimulus, the other hand passes the median line.
- Score M = 3 instead of 4 if during flexion of the arm two of the following criteria are also met: extension of the legs, occasionally also endorotation of the arm, interposition of the thumb between the fingers, maximal flexion of the wrist.

Appendix 3

Post-Acute Level of Consciousness Scale (PALOC-s)

Throughout the thesis this scale will further be referred to as LoC: Level of Consciousness

The reliability and validity of the PALOC-s: a Post-Acute Level of Consciousness scale for assessment of patients with prolonged disturbed consciousness after brain injury.

Eilander, H. J., Wiel, M., van de, Wijers, M., Buljevac, D., Lavrijsen, J. C. M., Hoenderdaal, P. L., Wijnen, V. J. M., Scheirs, J. G. M., Kort, P. L. M., de, & Prevo, A. J. H. (In press)

Global Level	*Score*	Description of the levels
Coma	Eyes are closed all the time. No sleep-wake cycles present.	
	1	All mayor body functions such as breathing, temperature control, or blood pressure can be disturbed. Generally, no reactions are noticed after stimulation. Sometimes reflexes (stretching or flexing) can be observed as a reaction when strong pain stimuli have been applied. No other reactions present.
Vegetative State (VS)	Patient has some sleep-wake cycles, but no proper day-night rhythm. Most of the body functions are normal. No further ventilation is required for respiration.	
	2	**Very little response (hyporesponsive)** Generally no response after stimulation. Sometimes delayed presentation of reflexes is observed.
	3	**Reflexive state** Often stimuli result in massive stretching or startle reactions, without proper habituation. Sometimes these reactions evaluate into massive flexing responses. Roving eye movements can be seen, without tracking. Sometimes grimacing occurs after stimulation.
	4	**High active level and/or reactions in stimulated body parts** Generally spontaneous undirected movements. Retracting of a limb following stimulation. Orienting towards a stimulus, without fixating. Following moving persons or objects, without fixating.
Minimally Conscious State (MCS)	Patient remains awake most of the day.	
	5	**Transitional state** Following and fixating of persons and objects. Generally more directed reactions to stimuli. Behaviour is automatic, i.e. opening of the mouth when food is presented, or reaching towards persons or objects. Sometimes emotional reactions are seen such as crying or smiling towards family or to specific (known) stimuli.
	6	**Inconsistent reactions** Sometimes, but not always, obeying simple commands. Totally dependent. Patient has profound cognitive limitations; neuropsychological testing is impossible. Level of alertness is fluctuating, but in general low.
	7	**Consistent reactions** Patient obeys simple commands. The level of alertness is high and stable. Many cognitive disturbances remain. Patient is totally dependent.
Consciousness	8	Patient is alert and reacts to his/her environment spontaneously. Functional understandable mutual communication is possible, sometimes with technical support. As yet, cognitive and behavioural disturbances can be present.

Appendix 4

Western Neuro Sensory Stimulation Profile (WNSSP)

A tool for assessing slow-to-recover head-injured patients.
Ansell, B.J., Keenan, J.E., and de la Rocha, O. (1989).

The total score on the WNSSP is the sum over all 33 items and represents a patient's overall cognitive/communicative performance. The maximum score possible is 113. Six subscales have been delineated which assess specific aspects of a patient's behaviour and provide a means for evaluating a patient's pattern of response. The subscales evaluate:

I. Arousal/Attention
II. Auditory Comprehension
III. Visual Comprehension
IV. Visual Tracking
V. Object Manipulation
VI. Expressive Communication

I. AROUSAL/ATTENTION

1. **Arousability : Ease of arousal at beginning of evaluation.**
   0 = Requires repeated presentation of 2 or more stimuli
   1 = Requires 2 or more stimuli
   2 = Requires 1 stimulus
   3 = Already awake
2. **Wakefulness: Longest period of time patient remains awake without being re-aroused.**
   0 = 10 minutes or less
   1 = 11-20 minutes
   2 = 21 or more minutes
3. **Eye Contact: Patient's gaze during the majority (50%) of the session.**
   0 = Closed
   1 = Open
   2 = Focused on examiner (>50%)
   9 = Physically unable to open eyes
4. **Attention to Task: Patients ability to attend to tasks.**
   0 = Less than 50%
   1 = 50% or more

Stimulus *= any sensory input including but not limited to voice, touching patient's arm, shaking patient, raising/lowering head of bed, applying wet cloth to patient's face.*

II. AUDITORY RESPONSE

Localization

5. Voice: Patient's response to introductory remarks at beginning of assessment.
6. Sound: Patient's best response to non-verbal sound during the evaluation (e.g. a bell out of patient's visual field).
   0 = No response
   1 = Undifferentiated response
   2 = Differentiated response

Comprehension

7-12. **Auditory Commands: Patient's ability to follow single-stage auditory commands (Shake my hand; Open/close your mouth; Stick out your tongue; Open/close your eyes; Raise your eyebrows; Move 'body part').**
   0 = No response
   1 = Incorrect response
   2 = Cued, delayed response
   3 = Cued, prompt response
   4 = Spontaneous, delayed response
   5 = Spontaneous, prompt response

Undifferentiated *= Same or similar response seen to all stimuli.*
Examples: generalized body movement, increased respiration, eye blinking, chewing, reflexive posturing.
Differentiated *= Different responses seen to various stimuli.*
Examples: eye movement or head turn to stimulus, movement of body part named or touched.
No response *= Patient does not respond within 20 seconds of presentation of stimulus.*
Delay *= Response occurs more than 5 seconds after stimulus has been presented.*
Cue *= Response occurs after more than one repetition of stimulus, presentation of visual model, tactile stimulation, or guided movement of appropriate body part.*

III. EXPRESSIVE COMMUNICATION

13. **Vocalization: Patient's best vocal utterance.**
   0 = No response
   1 = Spontaneous, non-meaningful **vocalization**
   2 = Spontaneous, meaningful **verbalization**
   3 = Vocalizes on command; mouths words or verbalizes **appropriately**
14. **Facial/Gestural Communication: Patient's use of facial expression and gesture for communication.**
   0 = No response
   1 = Uses one gesture or facial expression with at least primitive communicative intent

2 = Uses more than one gesture or facial expression with communicative intent

15. Yes/No Response: Patient's ability to produce differentiated "yes" and "no" responses.

0 = Neither reponse observed

1 = Either "yes" or "no"

2 = Both responses observed

Non-meaningful vocalization *= moaning, sighing, crying, other vocal noises*

Inappropriate verbalization *= speech which is either irrelevant to the stimulus or unintelligible.*

Vocalization on command *= repetition of sound or word*

Appropriate verbalization *= intelligible, relevant speech*

IV. VISUAL RESPONSE

Localization

16.– 19. Horizontal Tracking: Patient's ability to follow stimuli visually through the left and right visual fields (e.g. mirror, picture, object, individual).

0 = No reponse

1 = Midline to 1 side

2 = Midline to both sides

3 = Across midline

20. – 22. Vertical Tracking: Patient's ability to follow stimuli visually through the upper and lower visual fields (e.g. mirror, picture, object, individual).

0 = No response

1 = One direction

2 = Both directions

Comprehension

23. – 27. Written Commands: Patient's ability to follow single stage written commands (Shake my hand; Open/close your mouth; Stick out your tongue; Open/close your eyes; Raise your eyebrows; Move 'body part').

0 = No response

1 = Incorrect response

2 = Cued, delayed response

3 = Cued, prompt response

4 = Spontaneous, delayed response

5 = Spontaneous, prompt response

V. TACTILE RESPONSE

Localization

28. Touch: Patient's best response to tactile stimulation.

0 = No responses

1 = Undifferentiated response

2 = Differentiated response

29. Oral Stimulation: Patient's response to stimulation of the lips (with q-tip).

0 = Withdrawal/abnormal reflexes present

1 = Primitive reflexes present

2 = Tolerates stimulation

Abnormal reflexes *= tonic bite, tongue thrust, jaw thrust, withdrawal, lip retraction or pursing.*

Primitive reflexes *= rooting, sucking, phasic bite (chewing).*

Comprehension

30. – 32. Object Manipulation: Patient's ability to demonstrate conventional use of common objects (e.g spoon, comb, pencil).

0 = No response

1 = Holds/releases object

2 = Moves object/uses inappropriately

3 = Reaches/pushes away object

4 = Uses appropriately cued

5 = Uses appropriately spontaneously

9 = Both arms casted or splinted

VI. OLFACTORY RESPONSE

33. Smell: Patient's response to olfactory stimuli (various odors, pleasant and unpleasant).

0 = No response

1 = Undifferentiated response

2 = Differentiated response

9 = Not applicable (tracheostomy)

Appendix 5

Disability Rating Scale (DRS)

Disability Rating Scale for severe head trauma: coma to community
Rappaport, M., Hall, K.M., Hopkins, K., Belleza, T., and Cope, D.N.(1982)

		Score
I AROUSABILITY, AWARENESS, AND RESPONSIVITY		
1. Eye opening	Spontaneously	0
	To speech/sensory	1
	To pain	2
	None	3
2. Best verbal response	Oriented	0
	Confused	1
	Inappropriate	2
	Incomprehensible	3
	None	4
3. Best motor response	Obeying	0
	Localizing	1
	Withdrawing	2
	Flexing	3
	Extending	4
	None	5
II. COGNITIVE ABILITY FOR SELF-CARE ACTIVITIES		
4. Cognitive ability for feeding	Complete	0
	Partial	1
	Minimal	2
	None	3
5. Cognitive ability for toileting	Complete	0
	Partial	1
	Minimal	2
	None	3
6. Cognitive ability for grooming	Complete	0
	Partial	1

	Minimal	2
	None	3

III. DEPENDENCE ON OTHERS

7. Level of functioning	Completely independent	0
	Independent in special environment	1
	Mildly dependent	2
	Moderately dependent	3
	Markedly dependent	4
	Totally dependent	5

IV. PSYCHOSOCIAL ADABTABILITY FOR AGE-RELATED WORK RESPONSIBILITIES

8. Employability	Not restricted	0
	Selected jobs, competitive	1
	Sheltered workshop	2
	Not employable	3

Disability Rating Scale in categories (DRScat[1])

DRScat	TOTAL SCORE	LEVEL OF DISABILITY
1	0-1	None to Mild
2	2-3	Partial
3	4-6	Moderate
4	7-11	Moderately severe
5	12-16	Severe
6	17-21	Extremely severe
7	22-29	Vegetative state
8	30	Death

[1] Slightly changed version of the categories as proposed by Rappaport et al (1982).

Appendix 6

Glasgow Outcome Scale Extended (GOSE)

Structured interviews for the Glasgow Outcome Scale and the Extended Glasgow Outcome Scale: guidelines for their use

Wilson JTL, Pettigrew LEL, Teasdale G (1998)

CONSCIOUSNESS

1. Is the head injured person able to obey simple commands, or say any words

1 = No (VS)

2 = Yes

Anyone who shows ability to obey even simple commands, or utter any word or communicate specifically in any other way is no longer considered to be in the vegetative state. Eye movements are not reliable evidence of meaningful responsiveness. Corroborate with nursing staff. Confirmation of VS requires full assessment as in the Royal College of Physician Guidelines.

INDEPENDENCE IN THE HOME

2a. Is the assistance of another person at home essential every day for some activities of daily living?

1 = No

2 = Yes

For a 'No' answer they should be able to look after themselves at home for 24 hours if necessary, though they need not actually look after themselves. Independence includes the ability to plan for and carry out the following activities: getting washed, putting on clean clothes without prompting, preparing food for themselves, dealing with callers, and handling minor domestic crises. The person should be able to carry out activities without needing prompting or reminding, and should be capable of being left alone overnight.

2b. Do they need frequent help or someone to be around at home most of the time?

1 = No (Upper SD)

2 = Yes (Lower SD)

For a 'No' answer they should be able to look after themselves at home for up to 8 hours during the day if necessary, though they need not actually look after themselves.

2c. Was assistance at home essential before the injury?

1 = No

2 = Yes

INDEPENDENCE OUTSIDE THE HOME

3a. Are they able to shop with assistance?

1 = No (Upper SD)

2 = Yes

This includes being able to plan what to buy, take care of money themselves, and behave appropriately in public. They need not normally shop, but must be able to do so.

3b. Were they able to shop without assistance before the injury?

1 = No

2 = Yes

4a. Are they able to travel locally without assistance?

1 = No (SD)

2 = Yes

They may drive or use public transport to get around. Ability to use a taxi is sufficient, provided the person can phone for it themselves and instruct the driver.

4b. Were they able to travel without assistance before the injury?

1 = No

2 = Yes

WORK

5a. Are they currently able to work to their previous capacity?

1 = No

2 = Yes

If they were working before, then their current capacity for work should be at the same level. If they were seeking work before, then the injury should not have adversely affected their chances of obtaining work or the level of work for which for which they are eligible. If the patient was a student before injury then their capacity for study should not have been adversely affected.

5b. How restricted are they?

a) Reduced work capacity?

b) Able to work only in a sheltered workshop or non-competitive job, or currently unable to work.

1 = a (Upper MD)

2 = b (Lower MD)

5c. Were they either working or seeking employment before the injury (answer 'yes') or were they doing neither (answer 'no') ?

1 = No

2 = Yes

SOCIAL & LEISURE ACITIVITIES

6a. Are they able to resume regular social and leisure activities outside home?

1 = No

2 = Yes

They need not have resumed al their previous leisure activities, but should not be prevented by physical or mental impairment. If they have stopped the majority of activities because of loss of interest or motivation then this is also considered a disability.

6b. What is the extent of restriction on their social and leisure activities?

a) Participate a bit less: at least half as often as before injury

b) Participate much less: less than half as often

c) Unable to participate: rarely, if ever, take part

1 = a (Lower GR)

2 = b (Upper MD)

3 = c (Lower MD)

6c. Did they engage in regular social and leisure activities outside home before the injury?

1 = No

2 = Yes

FAMILY & FRIENDSHIP

7a. Have there been psychological problems which have resulted in ongoing family disruption or disruption to friendships?

1 = No

2 = Yes

Typical post-traumatic personality changes: quick temper, irritability, anxiety, insensitivity to others, mood swings, depression, and unreasonable or childish behaviour.

7b. What has been the extent of disruption or strain?

a) Occasional – less than weekly

b) Frequent – once a week or more, but tolerable

c) Constant – daily and intolerable

1 = a (Lower GR)

2 = b (Upper MD)

3 = c (Lower MD)

7c. Were there problems with family or friends before the injury?

1 = No

2 = Yes

If there were some problems before injury, but these have become markedly worse since injury then answer 'No' to Q7c.

RETURN TO NORMAL LIFE

8a. Are there any other current problems relating to the injury which affect daily life?

1 = No (Upper GR)

2 = Yes (Lower GR)

Other typical problems reported after head injury: headaches, dizziness, tiredness, sensitivity to noise or light, slowness, memory failures, and concentration problems.

8b. Were similar problems present before the injury

1 = No

2 = Yes

If there were some problems before injury, but these have become markedly worse since injury then answer 'No' to Q8b.

SCORING

The patient's overall rating is based on the lowest outcome category indicated on the scale.

1	Dead
2	Vegetative state
3	Lower severe disability (lower SD)
4	Upper severe disability (upper SD)
5	Lower moderate disability (lower MD)
6	Upper moderate disability (upper MD)
7	Lower good recovery (lower GR)
8	Upper good recovery (upper GR)

Appendix 7

The patient group

This Appendix extensively describes the patients who participated in the studies reported in this thesis. The table (at the end of this Appendix) presents a concise summary of the clinical details of the patients, from the moment of injury to discharge from the Early Intensive Neurorehabilitation. Programme (EINP), according to the observational scales described in the preceding Appendices. The clinical presentation and the acute management are described as obtained from the medical documents, and from the initial Computerised Tomography (CT) or Magnetic Resonance Imaging (MRI). Their progress (if any) is portrayed in terms of recovery to consciousness. In addition, the indication for the follow up track is given, irrespective whether the patient really did follow this track.

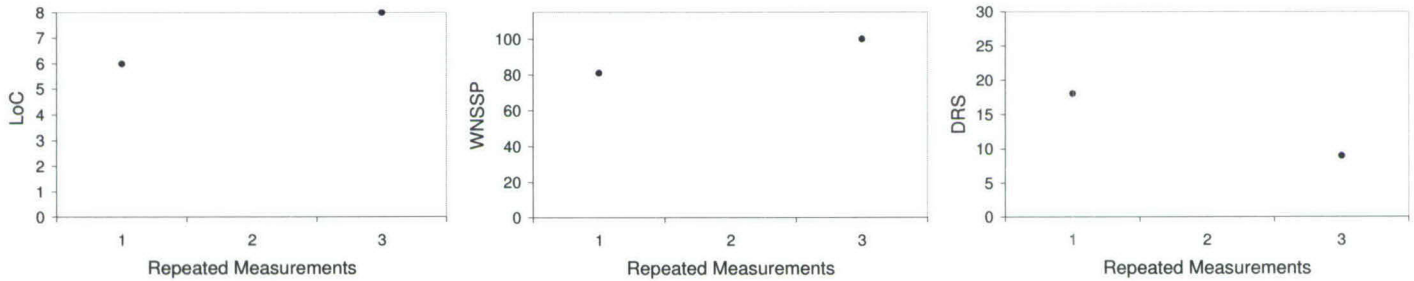
First, the clinical presentation of each patient is described, followed by the progress during the EINP. Because the data were collected retrospectively, the amount of information differs among patients. Regarding the rehabilitation progress some prominent information is presented.

An initial CT-scan or MRI-scan was received for 25 patients. For these patients a representative slice is presented of one of the scans with corresponding CT-score. When reported without further notice, it concerns the initial scan, made on the day of the injury. Unless indicated otherwise the scans are presented by the neurological convention in which the left brain appears on right side of the image. Some of the scans are not presented because of illegibility after copying to the (photographical) software, but their scores were used and presented in the table. The CT scores were only applied to the initial CT scans of theTBI patients.

The numbers assigned to the patients in the current chapter are used throughout this thesis.

Clinical presentation and acute management

Patient 1 was a woman who was 25 years old at the time of her injury. She was injured while driving a car, by hitting a tree with high speed. She was found unconscious at the scene of the accident, where her GCS was E1M2V1. She was intubated by a paramedic at the scene of the accident, transferred to hospital, and admitted to the Intensive Care Unit (ICU). Initial CT brain scanning showed a diffuse swollen brain with compressed basal cisterns and multiple punctuate haemorrhages, especially right frontal and right cerebellar. Patient 1 spent 14 days at the ICU. Subsequently, she was transferred to the neurology section, where she suffered from pneumonia. An endotracheal tube was applied, and she was fed by a percutaneous endoscopic gastrotomy infusion (PEG). She started to show spontaneous eye opening and localisation to pain, and started to make some sound now and then. Patient 1 was transferred to the RCL 40 days after injury (1 day after registration to EINP).



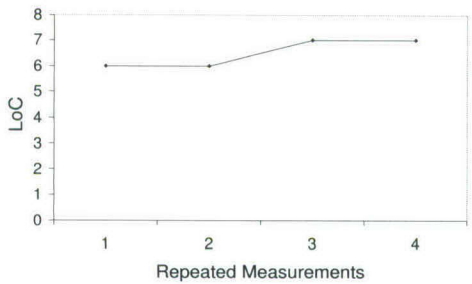
Rehabilitation programme and progress

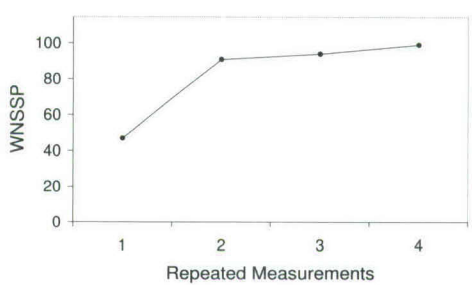
On admission patient 1 was already able to track with her eyes, and appeared to be able to hear. The swallow reflex was present and she was trained oral feeding. At the end of January the endotracheal tube was removed. When she was not stimulated, she showed involuntary, uncontrolled movements. She showed great progress during the EINP, except for the motor functions on her left side. She was able to recognise, and to name objects, and to name their function. Patient 1 suffered from a central hearing disturbance. In addition, she was suffering from fears, hallucinations, and delusions (e.g. hearing voices at night). Soon she started talking; however, the articulation was somewhat unclear. She was able to eat by herself, and was able to help with her self care activities (grooming). There were some cognitive disturbances, especially with respect to short-term memory. Patient 1 was disoriented in time and place. She showed some depressed mood fluctuations.

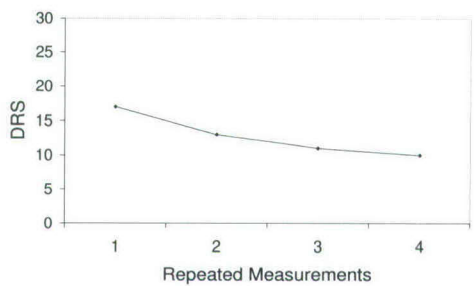
She was discharged 62 days after admission to EINP, indicated for regular rehabilitation.

Clinical presentation and acute management

Patient 2 was a woman who was 23 years old at the time of her injury. She was injured as a result of an explosion. She was found unconscious at the scene of the accident, where her GCS was E3M2V1. She was intubated by a paramedic at the scene of the accident and transferred to a local hospital, then transferred on to a tertiary acute hospital and admitted to the ICU. Initial CT brain scanning demonstrated a haematoma in the septum, a peri-orbital haematoma, and a left temporal contusion. There was a high intracranial pressure. An electroencephalogram showed a diffuse hypofunctional pattern with a slow physiological activity. Patient 2 spent 28 days at the ICU, and 2 was transferred to the RCL 64 days after injury (18 days after registration to the EINP).





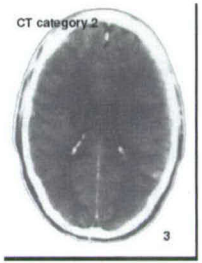


Rehabilitation programme and progress

Patient 2 soon started talking already and asking questions. She showed an insecure behaviour pattern, hanging forward with her head when she was failing in a task. She often gave up quickly and indicated that she was tired. Her answers were often socially desirable: 'It is ok, it does not matter'. She persevered into standard sentences, but this lessened in time. Patient 2 was very emotional, and at the end of the treatment period she showed some disinhibiting behaviour. She remained insecure about her actions, but was also very proud when she was able to finish a task.

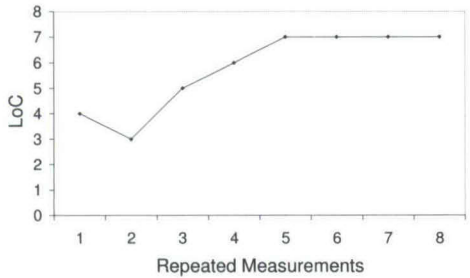
She showed some aphasic symptoms. She was able to read words, but not precisely. She also showed some orientation and memory problems. Her orientation of persons progressed, in contrast to her orientation problems with time and place. Therefore, she needed a lot of structure and overview on situations. Patient 2 also showed memory problems concerning her life prior to the injury

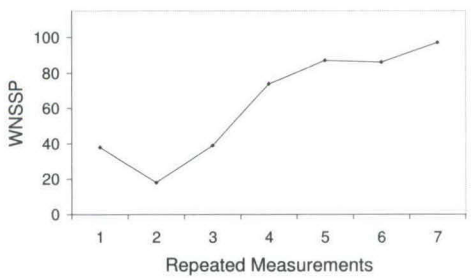
She was discharged 78 days after admission to the EINP, indicated for regular rehabilitation.

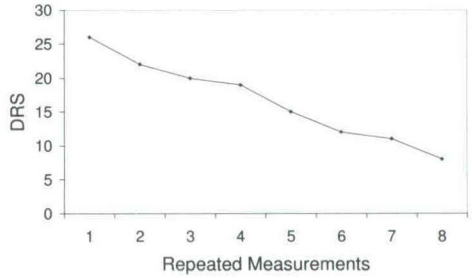


Clinical presentation and acute management

Patient 3 was a man who was 20 years old at the time of his injury. He was injured as a passenger during a traffic accident, being thrown out of the vehicle. He was found unconscious at the scene of the accident, where his Glasgow Coma Score was E1M1V1. He was intubated in the hospital and admitted to the ICU. There was a skull fracture. Initial CT brain scanning demonstrated diffuse axonal damage, and diffuse punctual haemorrhages, also in the brain stem. Patient 3 spent 60 days at the ICU. Patient 3 started to show some responses to the environment, obeying some commands. Patient 3 was transferred to the RCL 62 days after injury (7 days after registration to EINP).





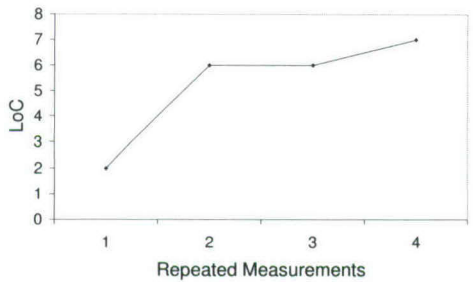


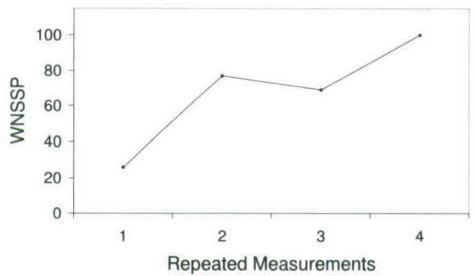
Rehabilitation programme and progress

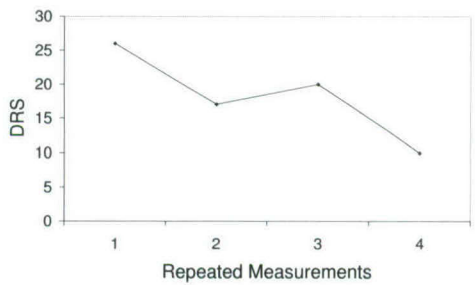
Initially, patient 3 was able to track with his left eye, while he was not able to open his right eye. He was able to turn his head into the direction of a sound. He was not able to swallow and was initially fed by a PEG infusion. He was able to move his left arm and showed a general hypertonic muscle tone. Patient 3 showed aggressive reactions to the environment when he became more conscious (LoC 5). His frustrated behaviour was a point of attention. He often would bang on his wheel chair table, with an open mouth and an angry expression. Especially when the limits of his abilities were reached or when the environmental input was too much. Because this behaviour was focused to specific situations, it was easy to diminish it. Later these behavioural expressions diminished, and he became friendlier. Patient 3 started to talk, initially whispering but later with a louder sound. He started to move his right arm and hand, yet mainly automatic movements. He was able to perform motor commands with his left arm and hand; however, it was difficult to plan his movements. In addition, his orientation of person, place and time were disturbed, and there were profound memory problems. He was discharged 126 days after admission to EINP, indicated for regular rehabilitation.

Clinical presentation and acute management

Patient 4 was a man who was 25 years old at the time of his injury. He was injured in a traffic accident, sitting at the back of a motorcycle without a helmet. He was found unconscious at the scene of the accident, where his GCS was E1M4V1. He was still deeply unconscious on admission at the hospital. Initial CT brain scanning demonstrated oedema at right parietal and left parietal frontal areas. There was a hypodensic lesion left in front of the temporal horn and right of the lateral ventricle. An extraventricular drain and a camino drain were applied. Patient 4 opened his eyes ten days after his injury. He spent 16 days at the ICU. Patient 4 was transferred to the RCL 42 days after injury (11 days after registration to EINP).



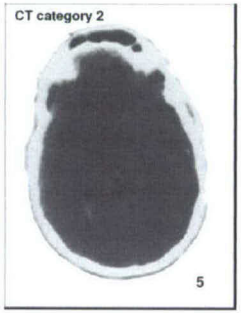




Rehabilitation programme and progress

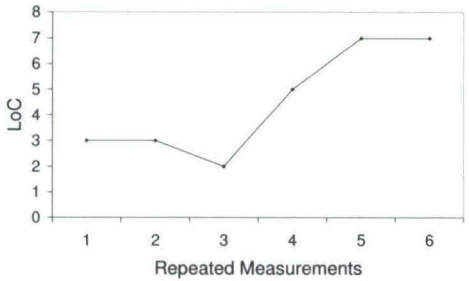
Initially patient 4 demonstrated some automatic behaviour patterns. He started talking about two months after his injury. Only with longer sentences he was difficult to understand. He repeated himself on request, however, got frustrated when he did not succeed. He also acted frustrated when he was told that his tasks were not performed right. Then he started talking loud and started banging on his wheelchair table. This anger was rather focused at situations than to persons. After such an episode he was difficult to motivate. Patient 4 showed large progress during the programme. He initiated talking and interacting with other people. He became more easily approachable and started making jokes and comments on a situation. He behaved very adult-like within the group. There were still cognitive problems at the end of the programme, such as memory problems, inhibited behaviour, and difficulties with structural acting and thinking.

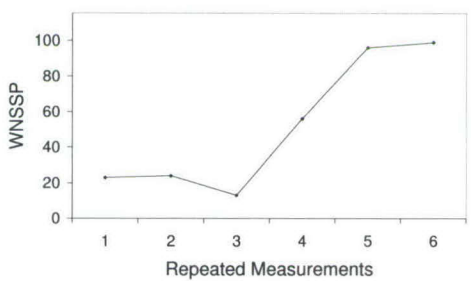
He was discharged 76 days after admission to EINP, indicated for regular rehabilitation.

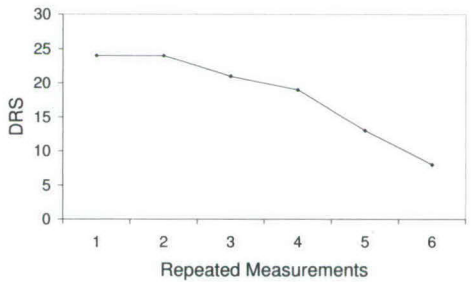


Clinical presentation and acute management

Patient 5 was a boy who was 17 years old at the time of his injury. He was injured in a traffic accident, hit by a car while driving a motorbike. He was intubated by a paramedic at the scene of the accident where his GCS was E1M1V1. He was then transferred to a local hospital, and admitted to the ICU, where his GCS was E1M3V1. Initial CT brain scanning demonstrated diffuse damage with intraventricular blood in the right temporal horn, and a mesencephalic contusion. A later CT scan showed a diffuse swollen brain with open basal cisterns and blood in the brain stem. Patient 5 spent 25 days at the ICU. An endotracheal tube and a PEG infusion were applied. Patient 5's level of consciousness slowly improved as he started to show some reactions to people. He was transferred to the RCL 40 days after injury (14 days after registration to the EINP).







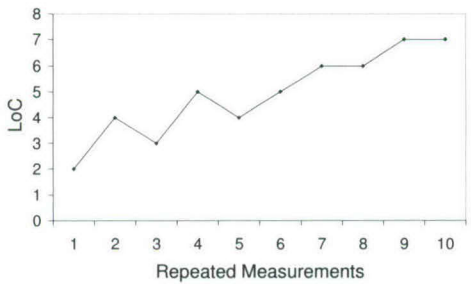
Rehabilitation programme and progress

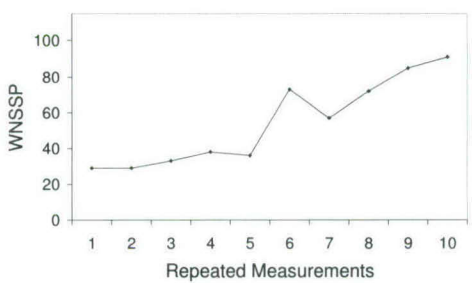
On admission, the right side of his body was hypertonic, and it developed less well compared to his left side. His left side was normotonic but atactic. His agitation increased with stimulation. He moved away from touch, and pushed aside objects. Soon he was able to give a yes/no response by nodding. His old knowledge appeared to be intact, however, but present knowledge was not. He did not know where he was, and what had happened. He often hung with his head forward and with his eyes closed, isolating himself from the environment. Two months after admission patient 5 became more motivated to work. He initiated conversations, and often started talking spontaneously. Initially he whispered, later he produced more sound and dysartry. He was able to construct short sentences and short answers. He showed difficulties in talking about his accident. He learned to transport himself with the wheel chair. His mood became better with more smiling. He learned to read full sentences, and his logical reasoning and memory improved. He was discharged 71 days after admission to the EINP, indicated for regular rehabilitation.

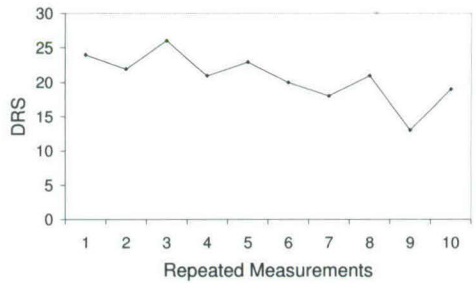
Clinical presentation and acute management

Patient 6 was a man of 20 years old at the time of his injury. He was injured in a traffic accident, driving with a car into a tree. His initial GCS was E2M4V2. He was intubated on the ICU. Initial CT brain scanning demonstrated diffuse axonal injury, and subcortical haemorrhages at the left and right side of the brain. There were skull fractures. His temperature and blood pressure were irregular. An intracranial pressure gauge was applied, and an endotracheal tube was applied.

His GCS progressed to E4M5/6V1. Patient 6 spent 23 days at the ICU. He showed some responses to commands with his left extremities, was more reactive to speech and had more wakeful periods. Patient 6 was transferred to the RCL 69 days after the injury (5 days after registration to the EINP).



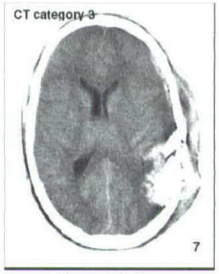




Rehabilitation programme and progress

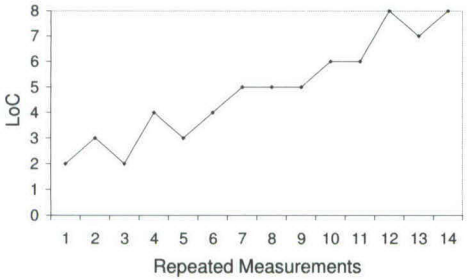
Initially, patient 6 was often tired and was lying in his bed for most of the time. He perspired a lot. Patient 6 showed a high tone but only few responses to the environment. Mostly he reacted to visual stimuli, and later to auditory stimuli. He showed a high tone when he was touched; more to the left than to the right.

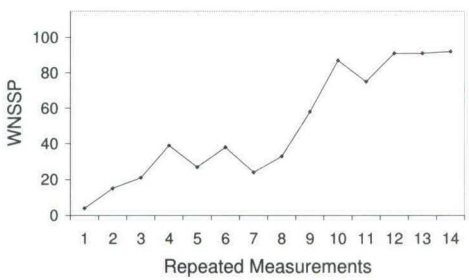
Later he showed progress. He started to make eye contact when communicating; initially showing clownish behaviour. He started to cooperate, yet depending on the given task. He often shut his eyes; it was not clear whether this was caused by fatigue or by the willing to isolate himself from the environment. He learned to give a yes/no response with his eyes, which was difficult because of his praxis problems. Therefore a twin talk and play-device was applied to his wheel chair. He was able to handle the device more and more adequately and consequently. He was discharged 133 days after admission to EINP, indicated for regular rehabilitation.

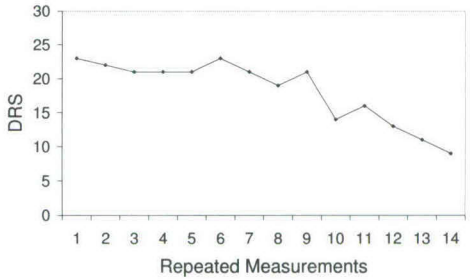


Clinical presentation and acute management

Patient 7 was a boy of 17 years old at the time of his injury. He was injured after joyriding under the influence of 0.3 promille alcohol, hitting a bridge. He was found unconscious at the scene of the accident, where his GCS was E1M4V2. He was intubated by a paramedic at the scene of the accident and transferred to hospital and admitted to the intensive care unit. Initial CT brain scanning demonstrated hypoxia, punctual haemorrhages, diffuse axonal injury, and a contusion to the brain stem. Some large haemorrhages were shown at left parietal, and right frontal and temporal areas. There were fractures to the jaw, the right mastoid, a perforation to the left ear, and an epidural haematoma. In addition, there was an impression fracture left parietally. The bone fragments were removed surgically. An MRI scan showed haemorrhagic contusions left temporo-parietally. The sulci were compressed and the basal cisterns more visible. The third ventricle was not visible very well. The midline shift was decreased. Patient 7 spent 20 days at the ICU. Small progress was seen: he opened his eyes to stimulation now and than, but no verbal response was seen. His GCS progressed to E3M4V1. Patient 7 was transferred to the RCL 39 days after injury (12 days after registration to the EINP).







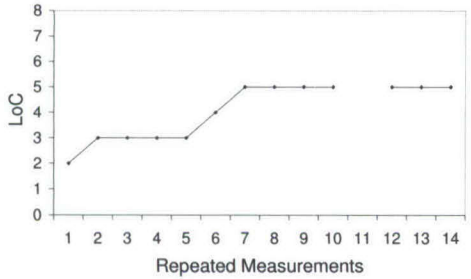
Rehabilitation programme and progress

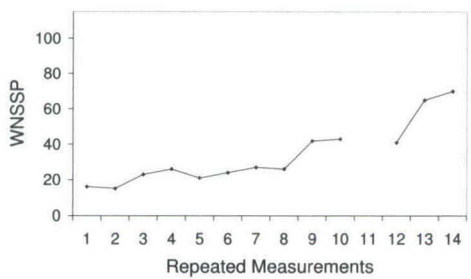
Initially, patient 7 showed little muscle tension. It was difficult to hang in the therapies, showing substantial reactions to pain during shoulder movement. He became very tired quickly, and he then started staring. He was not able to fixate to pictures or objects. Soon he was able to make eye contact for a while. Within this first period patient 7 learned to give a yes/no response with his eyes and nodding his head. He showed more motor responses. His facial mimic developed more and more, and he sometimes made some sounds. He started smiling and to look angry to people. He was able to show whether he liked something or not. There were periods in which he shut his eyes to isolate himself from the environment. During his recovery process, patient 7 showed resistance to the presented activities. He looked very angry; making threatening gestures, pushing away the material, and isolating himself by putting is hands in front of his face. He appeared disinhibited in his facial

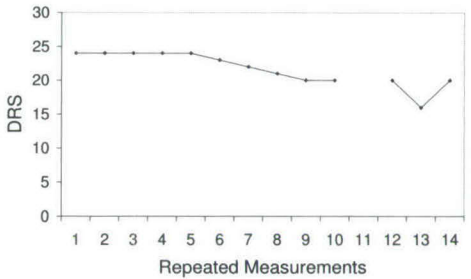
expression and body language. His behaviour could vary within a situation. It was not clear whether these changes were his real emotional intentions. Patient 7 slowly became more cooperative, and more directed to tasks. However, he displayed a dejecting and withdrawing impression. It appeared that patient 7 developed a depression, for which medication was administered. His mood became more positive within several days, however, there was still the tendency to act clownish, which made him difficult to handle. He was discharged 195 days after admission to EINP, indicated for further rehabilitation focused on the psychiatric and behavioural problems.

Clinical presentation and acute management

Patient 8 was a woman of 18 years old at the time of her injury. She was injured in a traffic accident as a passenger. She was thrown out of the vehicle, and was found unconscious at the scene of the accident, where her GCS was E1M3V1. She was moved to the ICU, where she was intubated and insufflated. Initial CT brain scanning demonstrated oedema, diffuse swelling of the brain, punctual haemorrhages, and diffuse white matter lesions. There were cortical and subcortical contusions to the left and right side of the brain. Patient 8 spent 11 days at the ICU. She showed firm flexion-extraction spasms to touch with some autonomic deregulations. Patient 8 was transferred to the RCL 31 days after injury (14 days after registration to the EINP).



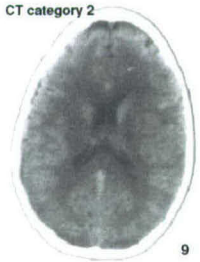




Rehabilitation programme and progress

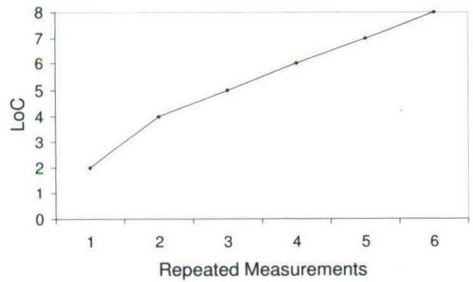
Initially, patient 8 showed progress in her physical condition. She moved away from intensive stimulation. She showed many spontaneous movements: turning of the head, moaning, tension, and shutting the eyes. She showed more eye contact over time. She would calm down when she was talked to. It was difficult to decide whether this agitation was caused by internal or external stimuli. Within this period it was important to offer one stimulus at the time, and to give her the time to response. Patient 8 showed a small progress. She learned to communicate via a communication button. She started to respond to spoken commands by pushing the yes or no button. Later she learned how to nod yes or no, however, these responses were not yet very adequate. Patient 8 still showed some agitation, which looked like a form of protest. There were periods of diminished consciousness.

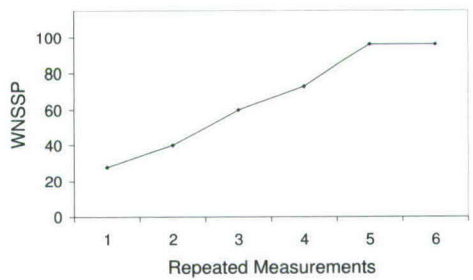
There was a perseveration in movements, vocalisation, and acting as a response to stimuli. She was discharged 182 days after admission to EINP, initially indicated for a nursing home.

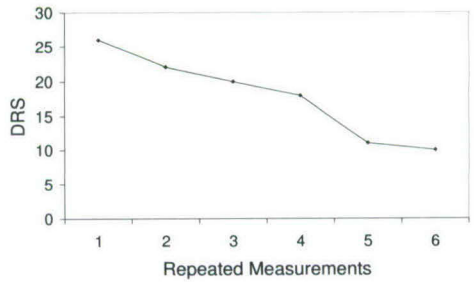


Clinical presentation and acute management

Patient 9 was a woman who was 25 years old at the time of her injury. She was injured in traffic accident, driving a motorcycle. At the time she arrived at the ICU her GCS was E1M3V2. Initial CT brain scanning demonstrated diffuse swelling of the brain, punctual and subarachnoidal haemorrhages, and cortical, subcortical and brain stem contusions on the left and right side of the brain. There was a skull fracture at the right occipital area. A camino pressure gauge and a thorax drain were applied. Because of a fracture of the dorsal vertebra, a halo-frame was applied. Patient 9 spent 16 days at the ICU. There was little neurological progress. Patient 9 was transferred to the RCL 38 days after injury (12 days after registration to EINP).







Rehabilitation programme and progress

Initially, patient 9 was very agitated, grasping to her clothes and to the halo frame. She reacted regularly to intensive sensory stimulation. Later, she started to perform some tasks. She needed some support, e.g. a demonstration by the therapist, performing the task together with the therapist, or pointing the body part that was involved in the task. Initially she neglected her right field of vision.

She started talking in short sentences, especially in the presence of family or friends. She was able to name pictures, and to read. She recognised her music and liked listening to it. With her left hand she learned to write and draw (copy). Often the letters were mixed up, or she perseverated in a particular letter. Eventually, it was difficult for her to talk about her accident. She was discharged 80 days after admission to EINP, indicated for regular rehabilitation.

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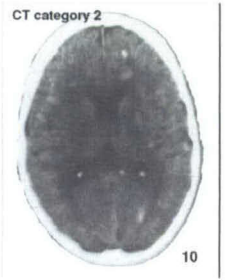
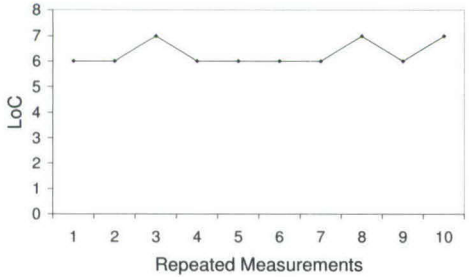
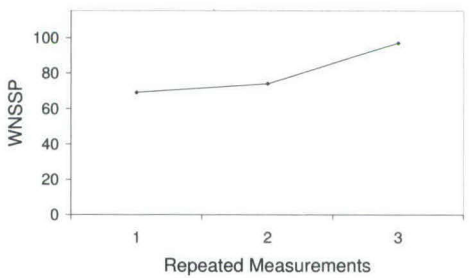


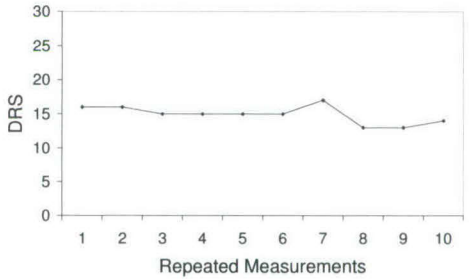
Clinical presentation and acute management

Patient 10 was a man of 25 years old at the time of his injury.

He was injured in a traffic accident, while driving a truck. He was found unconscious at the scene of the accident, where his GCS was E1M1V1. He was intubated by the helicopter team at the scene of the accident and transferred to the ICU. Initial CT brain scanning demonstrated punctual and intraventricular haemorrhages, and cortical and subcortical contusions on the left and right. A camino pressure gauge was applied. There were skull fractures to lateral orbital left and right areas. Further fractures were a bilateral mandible fracture, a subcapital humerus fracture on the left, a fracture to the left elbow, and a left femur fracture. During his stay at the ICU, patient 10 developed a fever, caused by a staphylococcus aureus infection. He spent 26 days at the ICU. An endotracheal tube was applied and he was fed via a nasogastric tube. His GCS slowly improved to E4M5Vt. Patient 10 was transferred to the RCL 59 days after injury (14 days after registration to the EINP).







Rehabilitation programme and progress

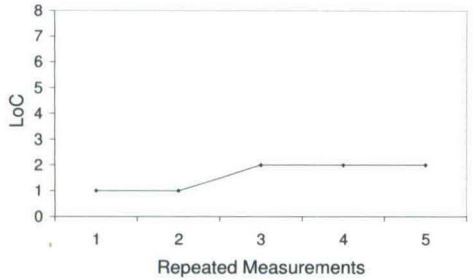
Initially, patient 10 showed progress in the recovery to consciousness. He showed, however, disinhibited behaviour, screaming, and throwing away the material presented during therapy. In the end of this period he started to act very passively, and communication was difficult to provoke. His answers were mainly restricted to yes and no nodding, or shrugging his shoulders. In particular, the patient was less responsive when subjected to a demanding approach.

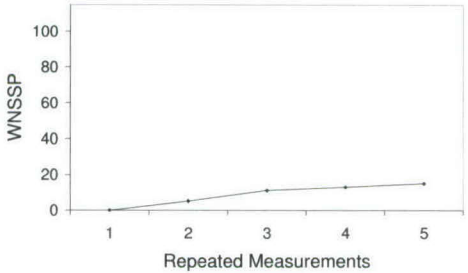
During his recovery, patient 10 was able to name pictures, obey to some commands, and to read words, however, these actions were not consequently evocable. Some conditioning processes took place, in which the patient acted with great resistance to particular situations and persons. This behaviour was difficult to stop. When he was asked to name the facial expressions on photos he only recognized the angry and happy faces. He would swear at the people on the photos, and refused to imitate the emotional expressions.

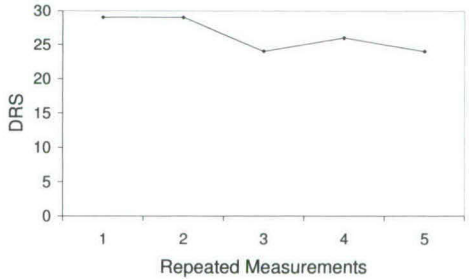
There were memory problems. He was able to reproduce information about his situation (where and why he was in the rehabilitation centre); however, it was difficult for him to bring some structure into thinking and acting. His orientation on place and person were disturbed. When there were no expectations on his acting, he would interact in a pleasant manner. In therapeutic situations, when there were expectations, his behaviour was more difficult. When the demands were to high, he stopped and started swearing, often offering apologies afterwards. The swearing mainly consisted of standard sentences. It was not clear whether this behaviour was caused by disinhibition or fear. He was discharged 118 days after admission to EINP, indicated for regular rehabilitation.

Clinical presentation and acute management

Patient 11 was a woman of 23 years old at the time of her injury. She was injured in a traffic accident. She was found unconscious at the scene of the accident, where her GCS was E1M2V4. She was intubated at the scene of the accident and transferred to the ICU. She was still deeply unconscious on admission on the hospital. Initial CT brain scanning demonstrated oedema, multiple contusions, and traumatic subarachnoidal haemorrhages. There also were skull fractures. Initial neurosurgical treatment consisted of the introduction of an external ventricular drain. An endotracheal tube was applied and she was fed via a nasogastric tube. A PEG infusion was applied. Her GCS progressed to E4M4V6. She performed some tasks on demand; however, her acting was doubtful. Her eyes were open widely, yet not focused. Artificial respiration was slowly ended. Some complications during the acute phase were pneumonia and a focal epileptic seizure. A follow up CT and MRI scan revealed an old subdural haematoma at the right frontal, and a contusion at the left occipital area. Later on, patient 11 was infected with MRSA (methicilline resistente staphylococcus aureus) bacteria. The last CT scan demonstrated central atrophy, temporal hypodensity, a subdural hygrom, a too large ventricle system, multiple hypodensities and contusions. Patient 11 spent 58 days at the ICU, and was transferred to the RCL 198 days after injury (111 days after registration to the EINP).



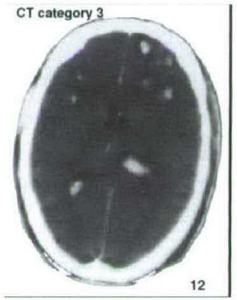




Rehabilitation programme and progress

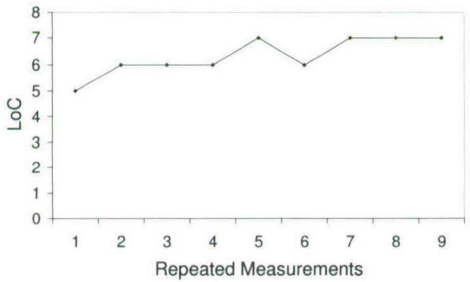
Initially, patient 11 was weak. Later her condition progressed a little; however, she nearly showed no reactivity to stimulation. Only pain stimuli lead to clear responses. Soon within her treatment it was decided that patient 11 showed no progress and the EINP was ended.

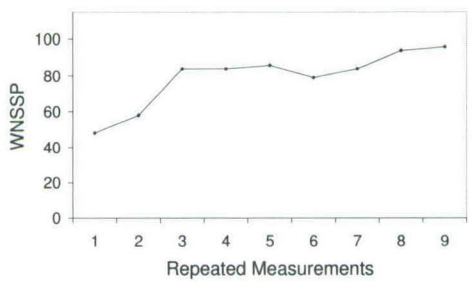
She was discharged 77 days after admission to EINP, indicated for a nursing home.

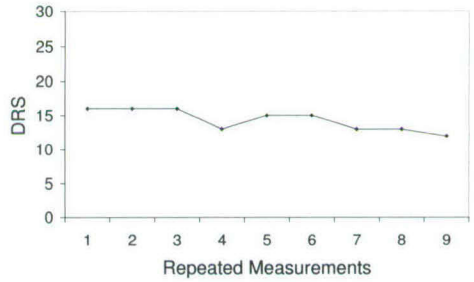


Clinical presentation and acute management

Patient 12 was a man who was 21 years old at the time of his injury. He was injured as a car driver, by hitting a tree with high speed. He was intubated at scene of the accident, transferred to hospital, and admitted to the intensive care. On admission to the hospital his GCS was E1M1V1. Initial CT brain scanning demonstrated multiple haemorrhages (bilateral frontal, left parietal and temporal, and left thalamic areas), diffuse swelling, oedema, hypoxia, and hydrocephalus. There was a left skull fracture. Patient 12 suffered pneumonia. Initial surgical treatment consisted of the application of a thorax drain. A bilateral temporoparietal craniotomy was performed. Patient 12 spent 57 days at the ICU, showing a GCS of E2M4t at the end if his stay. Patient 12 was transferred to the RCL 57 days after the injury (21 days after registration to the EINP).







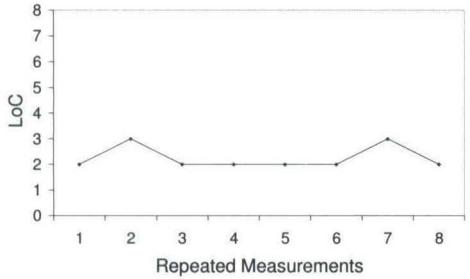
Rehabilitation programme and progress

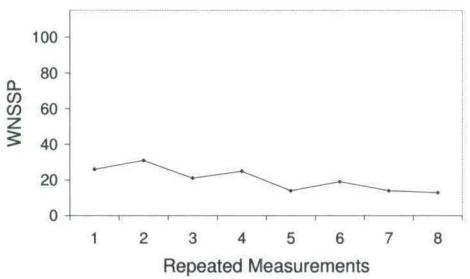
On admission to the RCL, patient 12 already spoke. Initially this was not very understandable, and soft, but his speech soon became louder. He started talking more and more on his own initiative. He showed a staring, faraway look. Later there was more eye contact. His behaviour became gradually more defensive and averted. He often refused to perform a task. He showed 'escaping behaviour', saying things like: 'I have to go', 'I do not have enough time'. He needed to be provoked, however, got irritated soon. Patient 12 often reacted oversensitively when touching certain materials, e.g. the door handle, which was too cold, according to him. Also the sounds of a therapist could irritate him. He reacted with standard sentences and defensive remarks. Often he considered the therapy material to be his own. His orientation capacities were variable: at one point he knew he was in a rehabilitation centre, at another point he was convinced of being at the MacDonald's. He confused the names of people, and days and months. Therefore, he needed much structure in his environment to feel safe. The defensive remarks gave him some feelings of control on the situation. He was discharged 119 days after admission to the EINP, indicated for regular rehabilitation.

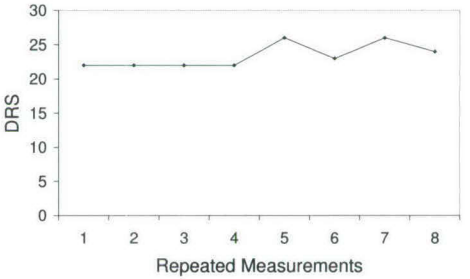
Clinical presentation and acute management

Patient 13 was a woman of 18 years old at the time of her injury.

She was injured in a traffic accident. She was found unconscious at the scene of the accident, where her GCS was E1M2V1. Initial CT brain scanning demonstrated oedema, diffuse brain swelling, hydrocephalus, punctuate and subarachnoidal haemorrhages, a diffuse white matter lesion, progressive atrophy, and contusion to the brain stem. An intracranial pressure gauge was applied. There were further fractures to the pelvis, mucosa, and teeth. An endotracheal tube was applied, and she was fed by a PEG infusion. Patient 13 spent 32 days at the ICU. She showed some responses to the environment by eye tracking and blinking the eyes. Patient 13 was transferred to the RCL 122 days after the injury (19 days after registration to the EINP).



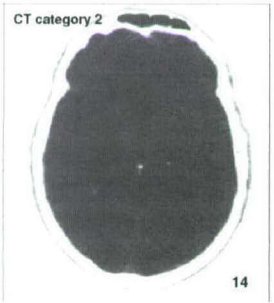




Rehabilitation programme and progress

Patient 13 sometimes reacted to stimulation with a general increase in body tone, gnashing her teeth, and turning with her head and feet. In particular, she reacted to pain, temperature and touch stimuli. There was no directed behaviour.

Patient 13 showed insufficient progress to continue EINP. She was discharged 108 days after admission to EINP, indicated for a nursing home.

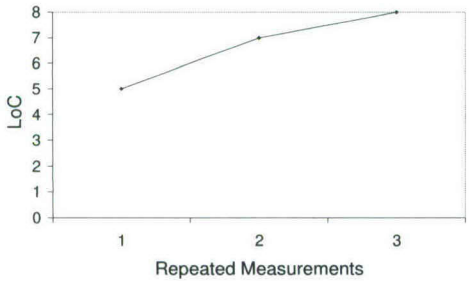


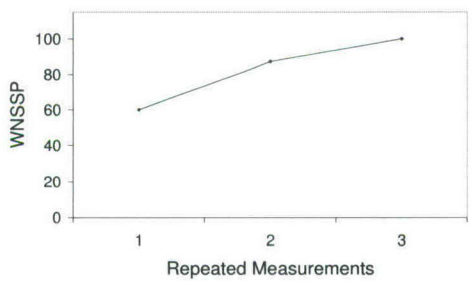
Clinical presentation and acute management

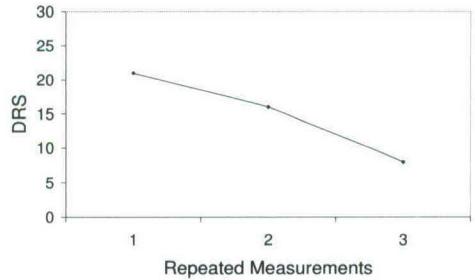
Patient 14 was a man of 21 years old at the time of his injury.

He was injured in a traffic accident. He was found unconscious at the scene of the accident with a rigid body posture, and a GCS of E1M2V1. The initial CT brain scanning demonstrated haemorrhages to the right occipital horn, oedema, diffuse brain swelling, hydrocephalus, ischeamia, and punctual haemorrhages. There was a skull fracture at the right orbita, and a contusion of the right lung.

Patient 14 spent 17 days at the ICU. An intracranial pressure gauge was applied, and an endotracheal tube was applied. At that moment his GCS progressed to E2M3Vt. Patient 14 was transferred to the RCL 79 days after his injury (53 days after registration to the EINP).



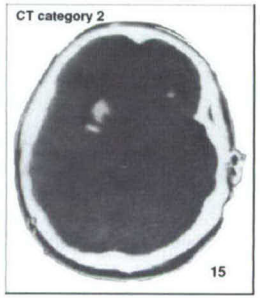




Rehabilitation programme and progress

Initially, patient 14 developed a high fever. Therefore he was returned to the ICU, and was treated for pneumonia. He returned to the RCL with an endotracheal tube again. Patient 14 made a good progress. He was able to perform tasks and to respond to commands. After removing the endotracheal tube, he was able to talk understandably. Soon oral feeding was trained. Patient 14 start to give adequate answers. He suffered some memory problems.

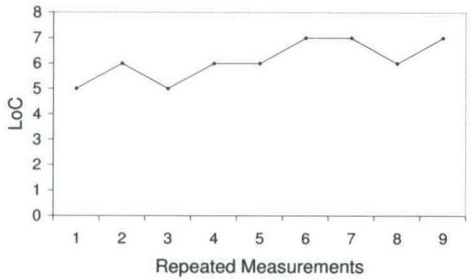
He was discharged 34 days after admission to EINP, indicated for regular rehabilitation.

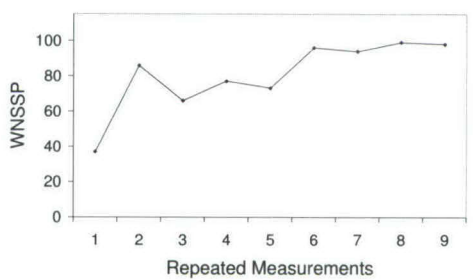


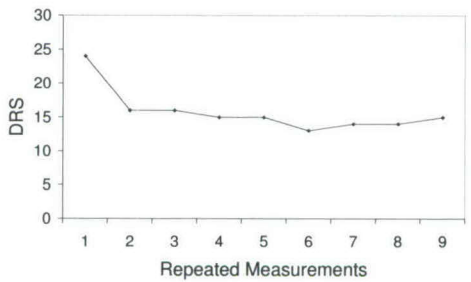
Clinical presentation and acute management

Patient 15 was a boy who was 17 years old at the time of his injury.

He was injured in a traffic accident. He was jammed in his car for about 60 minutes. He was found unconscious at the scene of the accident, where his GCS was E2M5V1. Initial brain scanning demonstrated multiple contusions frontally and temporally, high right parietal diffuse brain swelling, and punctual haemorrhages. There also was a skull fracture. Patient 15 did not show any communication with the environment. Sometimes he reacted to pain by crying. Gradually he showed some eye tracking. Patient 15 spent 21 days at the ICU. He was transferred to the RCL 73 days after his injury (34 days after registration to the EINP).

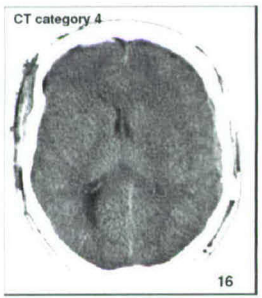






Rehabilitation programme and progress

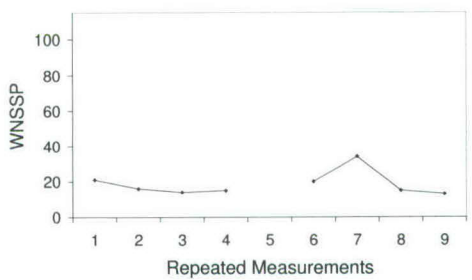
Initially, patient 15 talked negatively about himself, asking for feedback from the environment. He often used standard sentences, talking fast and inarticulately. There were problems on the areas of orientation, logical reasoning and initiative. He showed difficulties in the performance of tasks. He reacted restlessly, impulsively and (sexually) disinhibited. He complained a lot about feeling unwell, and wanted to stop with the tasks. He needed a lot of stimulation and encouragement from the environment. Later on, patient 15 started talking slower, and softer, and from time to time displayed a distracted, gazing look. He became more passive and lifeless, not showing any interest anymore. When he did not succeed he became angry, with some verbal and physical disinhibition. Some standard remarks were repeated in those situations: 'I want to stop now', 'I have to use the toilet', 'do I have to shoot you', 'I want to use the telephone'. When no reaction followed, he started swearing and hitting on his wheel chair table. This destructive behaviour and the additional problems in memory, attention, and concentration prevented his recovery. He was discharged 120 days after admission to the EINP, indicated for rehabilitation, focusing on his psychiatric problems.

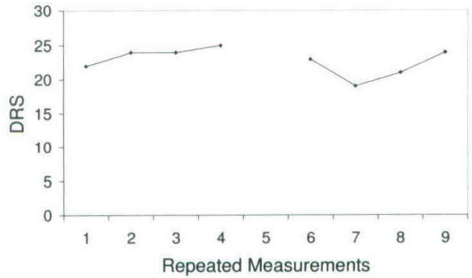


Clinical presentation and acute management

Patient 16 was a man of 25 years of age at the time of his injury.

He was injured in a traffic accident, and hit by a train. He was found unconscious at the scene of the accident, was intubated by the trauma team at the scene of the accident and transferred to a hospital and admitted to the intensive care unit. Initial CT brain scanning demonstrated a subdural haematoma left parietal and right frontal. There were skull fractures. Initial neurosurgical treatment consisted of the application of an intracranial pressure gauge, and a bilateral craniotomy. The haematoma was removed. In addition, an amputation of the lower limb was performed. Patient 16 spent 16 days at the ICU. His GCS progressed to E2M5V1, reacting to some stimulation. Patient 16 was transferred to the RCL 81 days after the injury (55 days after registration to the EINP).

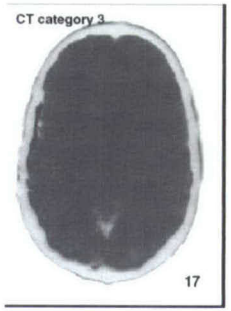




Rehabilitation programme and progress

Initially, patient 16 showed very little progress. Sometimes there were responses to pain, temperature and touch. He would respond with closing his eyes and chewing movements. He often showed a distracting, gazing look. Sometimes there was some tracking of the eyes to objects. He did not show any anticipating behaviour.

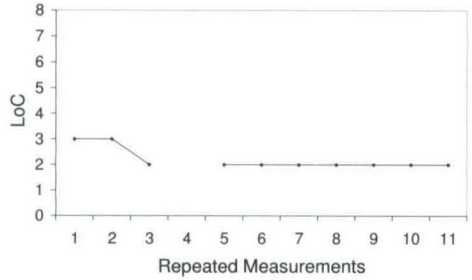
No progress was seen, and he was difficult to arouse. In July he suffered a large epileptic seizure. From there on he did not show any reaction to stimulation anymore. The EINP was no longer continued, and he was discharged 111 days after admission to EINP, indicated for a nursing home.

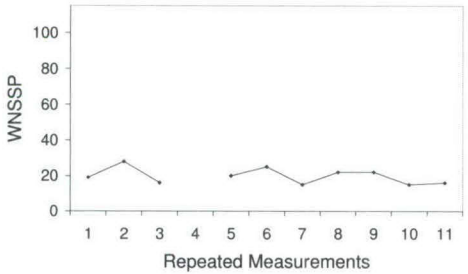


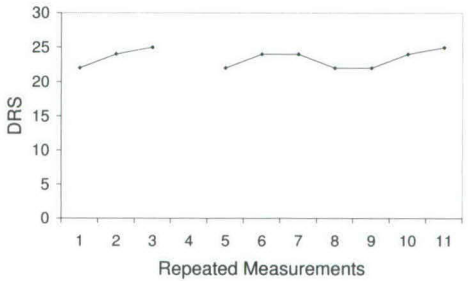
Clinical presentation and acute management

Patient 17 was a man who was 25 years old at the time of his injury.

He was injured as biker, hit by a car. He was found unconscious at the scene of the accident, where his GCS was E1M1V1. He was reanimated and intubated by a paramedic at the scene of the accident, transferred to the hospital and admitted to the intensive care unit. Initial CT brain scanning demonstrated an epidural haematoma on the right, open cisterns, and visible ventricles. Initial neurosurgical treatment consisted of the removal of the epidural haematoma. An intracranial pressure gauge was applied, as well as an endotracheal tube . After the operation patient 17 did not regain consciousness. Follow up CT scanning showed subarachnoid haemorrhages on the tentorium, and punctual haemorrhages on the pons and mesencephalon. In addition, there was diffuse white matter lesion, compressed basal cisterns, and small ventricles. Patient 17 spent 72 days at the ICU. His GCS progressed to E4M3Vt. The patient started to show some responding to the environment. Patient 17 was transferred to the RCL 80 days after the injury (28 days after registration to the EINP).





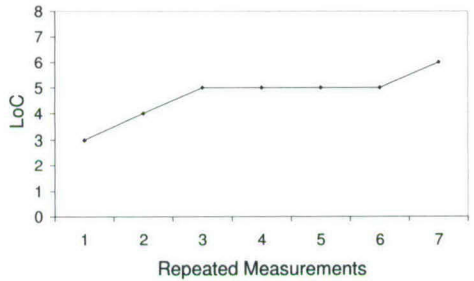


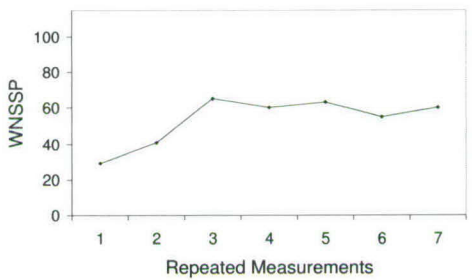
Rehabilitation programme and progress

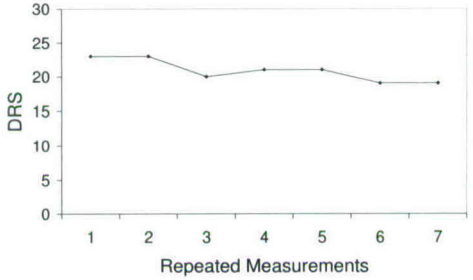
Patient 17 reacted to the stimulation with intensive movements, particularly to touch, temperature and loud sounds. He hardly showed avoidance responses. There were prolonged periods in which he closed his eyes. It was not clear whether this was caused by overstimulation, fatigue, or decreased alertness. Patient 17 showed insufficient progress, and EINP was no longer continued. He was discharged 139 days after admission to EINP, indicated for a nursing home.

Clinical presentation and acute management

Patient 18 was a boy of 6 years old at the time of his injury. He nearly drowned, and was pulled out of the water after fifteen minutes. He was resuscitated for about nine minutes. He was transferred on to a hospital and admitted to the intensive care unit, where his GCS was 5 at the maximum. He suffered hypothermia (32 degrees Celsius), and after warming up he developed a fever. Initial CT brain scanning demonstrated diffuse hypoxia and anoxia, as well as a diffuse white matter lesion. MRI scanning on showed diffuse hypoxia and ischemia, and subcortical damage to the white matter. An endotracheal tube was applied, and his GCS at that time was E1M2Vt. Patient 18 spent 8 days at the ICU, and was transferred to the RCL 56 days after the injury (28 days after registration to the EINP).







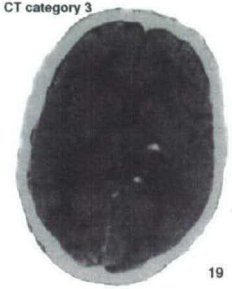
Rehabilitation programme and progress

The basic sensory stimulation programme was started. Initially it was unclear whether there were auditory problems. During the basic cognitive programme patient 18 showed progress, and he was able to work with the therapeutic material. However, his behaviour seemed automatic. He was especially focused on people and moving objects. Sporadically he spoke little words. He often smiled when he was being talked to. He was very easily distracted, and showed some problems in functional acting.

His level of consciousness soon progressed; however, there was still a disturbed processing of information. In addition, patient 18 suffered from dyspraxia.

He was discharged 83 days after admission to EINP, indicated for regular rehabilitation.

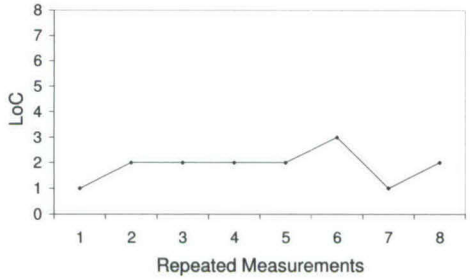
CT category 3

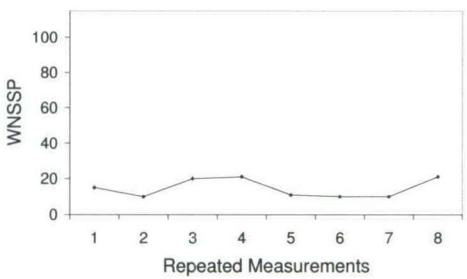


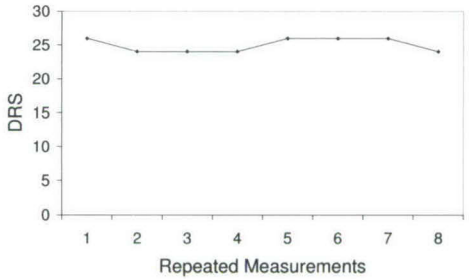
19

Clinical presentation and acute management

Patient 19 was a man of 21 years old at the time of his injury. He was injured in a traffic accident. He was transferred to a hospital and admitted to the intensive care unit. Initial CT brain scanning demonstrated punctuate and intracerebral haemorrhages, contusions, atrophy, hypodensity, diffuse white matter lesions. There was a skull fracture. There were further fractures to the clavicle, the femur, and ribs. An endotracheal tube was applied. Patient 19 spent 35 days at the ICU, and was transferred to the RCL 60 days after his injury (13 days after registration to the EINP).





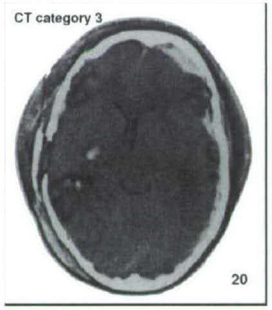


Rehabilitation programme and progress

Initially, patient 19 responded to sensory stimulation, particularly to extreme stimuli, e.g. touch, temperature, and pain. His responses consisted of an increase in muscle tone, turning of the head, chewing movements, and changes in facial mimic. He did not react to visual stimulation.

Little progress was seen during the treatment, e.g. eye tracking, and sometimes performing simple tasks. However, this behaviour was not consistent.

He was discharged 105 days after admission to EINP, indicated for a nursing home.

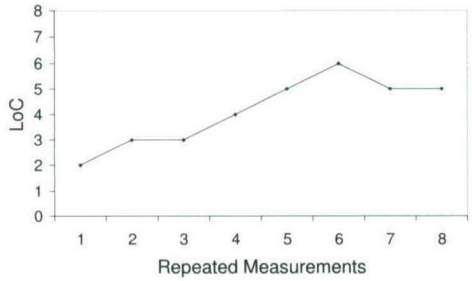


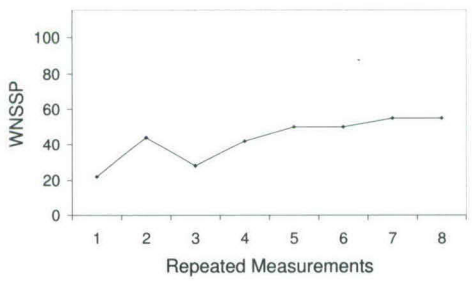
Clinical presentation and acute management

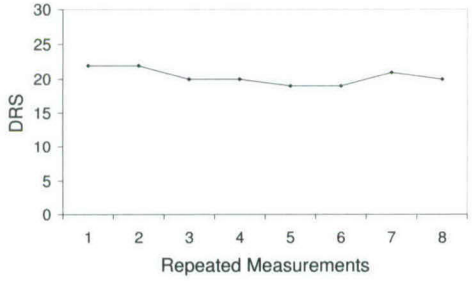
Patient 20 was a boy of 15 years old at the time of his injury.

He was injured in a traffic accident, as a scooter driver without a helmet. He was transferred to a hospital and admitted to the intensive care unit. Initial CT brain scanning demonstrated punctuate and intracerebral haemorrhages, contusions, atrophy, hypodensity, diffuse white matter lesions. There was a skull fracture, and more fractures to the clavicle, the femur, and ribs. An endotracheal tube was applied.

Patient 20 spent 33 days at the ICU, and was transferred to the RCL 136 days after his injury (68 days after registration to the EINP).



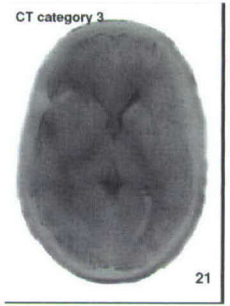




Rehabilitation programme and progress

Initially, patient 20 reacted only to touch and temperature stimulation. He hardly responded to auditory, visual, and olfactory stimulation. His responses were mainly changes in his respirations and mimic, and an increase in muscle tone. Sometimes he reacted with some sounds.

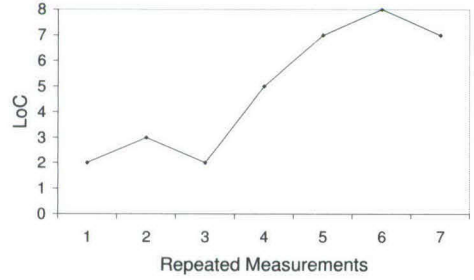
Patient 20 started to perform simple tasks, and he showed a yes/no response. Yet his reactions were not consistent. A combination of the sensory and cognitive stimulation programme was applied. He persevered into his actions. He was not able to talk, but could communicate via a minicam. He was able to understand people, and could produce simple words and answers to questions using the computer. His physical condition was still very bad. He was very difficult to motivate during the therapies. He was discharged 112 days after admission to EINP, indicated for a nursing home.

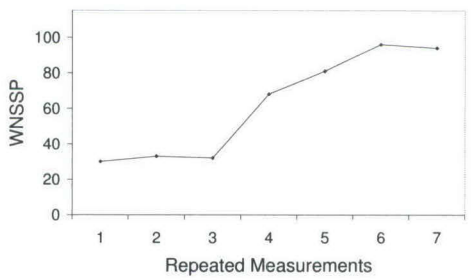


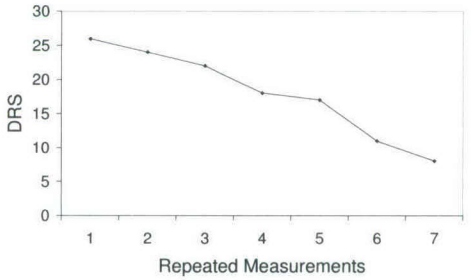
Clinical presentation and acute management

Patient 21 was a man of 25 years old at the time of his injury. He was injured in a traffic accident, driving a motorcycle and hitting a tree with high speed. He was found unconscious at the scene of the accident, where his GCS was E1M1V1. He was intubated by a paramedic at the scene of the accident, transferred to a hospital and admitted to the intensive care unit. Initial CT brain scanning demonstrated oedema, diffuse brain swelling, diffuse white matter lesions, punctual haemorrhages, and diffuse axonal damage. There was a skull fracture. Later scans showed blood in the ventricles. Initial neurosurgical treatment consistent of the application of a thorax drain and an endotracheal tube. Patient 21 spent 64 days at the ICU.

His GCS progressed to E4M6Vt. He was able to respond to commands of friends and family. Patient 21 was transferred to the RCL 64 days after his injury (34 days after registration to the EINP).







Rehabilitation programme and progress

Patient 21 was soon able to speak understandably and to make a conversation using a letter card. His performance improved when good instructions were given or when a therapist would demonstrate the task. When he did not succeed he was very quickly frustrated, and started to scream or pushing away the material.

His memory progressed. He was able to remember happenings, persons, and information. He was able to reason logically, asking questions and making remarks about his emotions and physical condition.

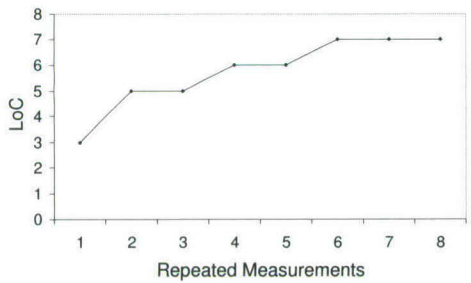
He was discharged 77 days after admission to the EINP, indicated for regular rehabilitation.

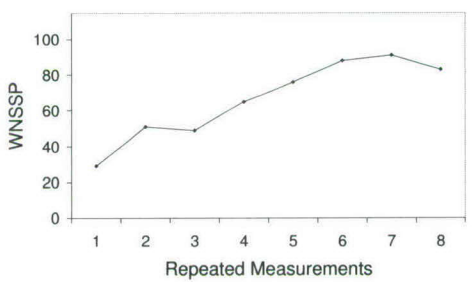

22

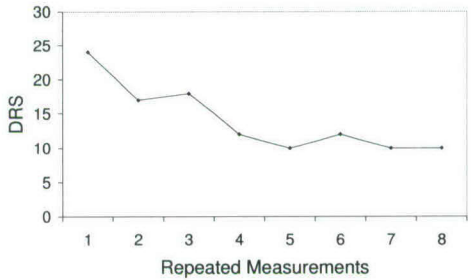
Clinical presentation and acute management

Patient 22 was a boy who was 8 years old at the time of his injury.

He suffered a brain haemorrhage. After a period of severe headaches, vomiting, and fever, his eyes turned backwards and his body was totally tensed. Patient 22 was intubated. He showed 'pinpoint' pupils. His GCS was E1M1Vt. It seemed to be a spontaneous haemorrhage for which no cause could be found. Initial CT scanning showed a large intracerebral haematoma left occipitoparietally, which expanded to the ventricles. In addition, a hydrocephalus was evident. Two drains were applied into the ventricles. A later MRI scan showed intraparenchymical haemorrhages occipitoparietally, and to the left thalamus and the corpus callosum. Patient 22 spent 33 days at the ICU. The drains were removed, and he developed bacterial meningitis. His GCS progressed to E5M5V2. He started to react in an agitated fashion to the environment. Sometimes he cried or smiled. Patient 22 was transferred to the RCL 81 days after his injury (52 days after registration to the EINP).





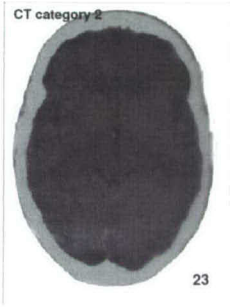


Rehabilitation programme and progress

Patient 22 showed good progress. His vision was disturbed, but his auditory reactions were good. He was able to answer questions. However, sometimes he was not able to talk. It was not clear whether this was caused by a decrease in alertness, or whether he did not understand the question.

Later he talked more often, also constructing longer sentences and making jokes. His memory progressed. He was able to remember names, situation, and the date. However, his logical reasoning was disturbed, and he showed anomia. In addition, patient 22 showed a vestibular sensitivity, resulting in frequently vomiting.

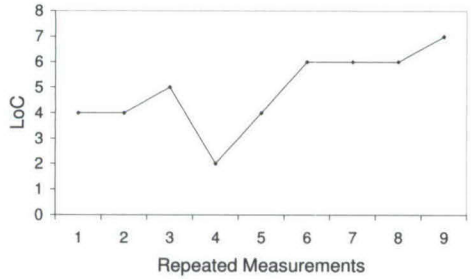
He was discharged 119 days after admission to the EINP, indicated for regular rehabilitation/nursing home.

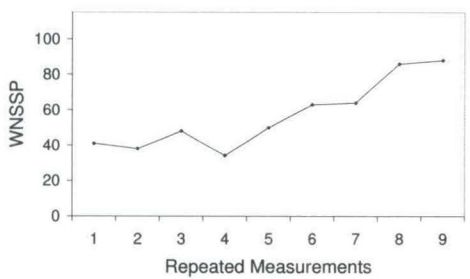


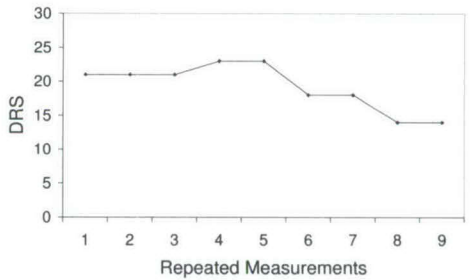
Clinical presentation and acute management

Patient 23 was a woman of 18 years old at the time of her injury.

She was injured in a traffic accident. She was found unconscious at the scene of the accident, where her GCS was E1M1V1. She was intubated by a paramedic at the scene of the accident, and a thorax drain was applied. Then she was transferred to the hospital and admitted to the intensive care unit. Initial CT brain scanning demonstrated oedema, diffuse brain swelling, and ischemia. An intracranial pressure gauge was applied. In addition, an endotracheal tube and a PEG infuse were applied. There were further injuries to the lungs, the liver, and the spleen. Her GCS progressed to E4M3V1. She did not show any directional response. Patient 23 spent 29 days at the ICU, and was transferred to the RCL 49 days after her injury (7 days after registration to the EINP).



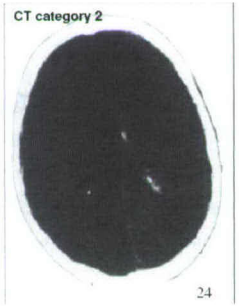




Rehabilitation programme and progress

Initially, patient 23 showed automatic responses, and needed much encouragement. She was often fatigued, and her condition was bad. It was decided to apply a rest period. After this period she showed great progress. She was more often alert, and stronger. She still needed encouragement to initiate her actions. When she was externally motivated by the therapist, and when there was structure in the tasks, she was able to perform them.

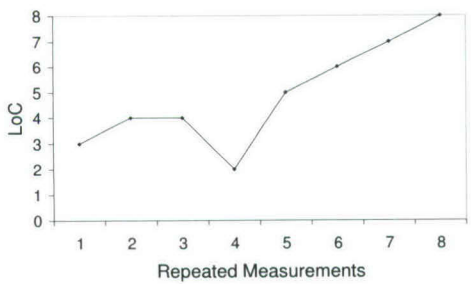
She was discharged 115 days after admission to the EINP, indicated for regular rehabilitation.

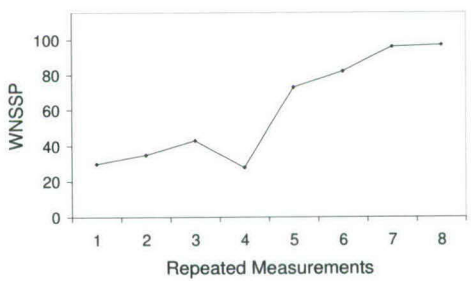


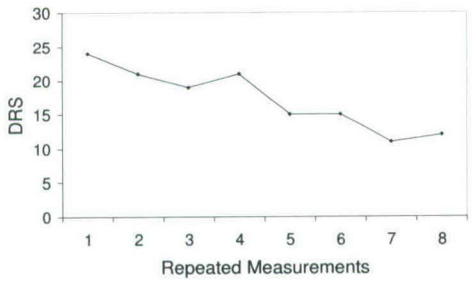
Clinical presentation and acute management

Patient 24 was a boy of 17 years old at the time of his injury.

He was injured in a traffic accident. He was found unconscious at the scene of the accident, where his GCS was E1M2V1. Initial CT brain scanning demonstrated oedema, intraventricular and intracerebral haemorrhages, left subcortical contusions, damage to the brain stem, and diffuse white matter lesions. His GCS progressed to E4M3V1. He did not show any directional response. Patient 24 spent 13 days at the ICU, and was transferred to the RCL 44 days after the injury (21 days after registration to the EINP).



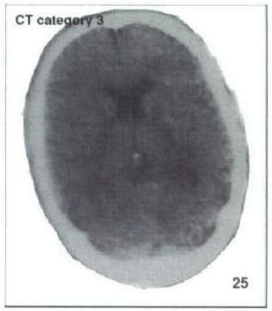




Rehabilitation programme and progress

Patient 24 showed great variability in his alertness, and was often difficult to keep awake. Within the first weeks there were periods of large agitation with physical excitation and very loud screaming, shrieking and screeching. Later on, he started to cooperate more and more. He started to talk understandably, made jokes, laughed about them, and took the initiative for a conversation more and more. The screaming lessened, however, he sometimes showed some anger when a task did not succeed. His speech was disturbed, because of severe dysartry and coordination disturbances in the mouth area. There were also problems with his memory and orientation, both for the short and long term. He could not remember new information.

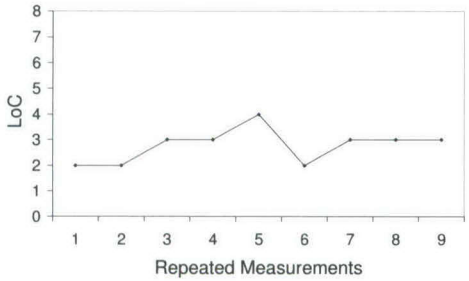
He was discharged 92 days after admission to the EINP, indicated for regular rehabilitation.

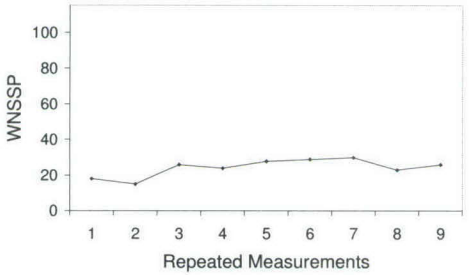


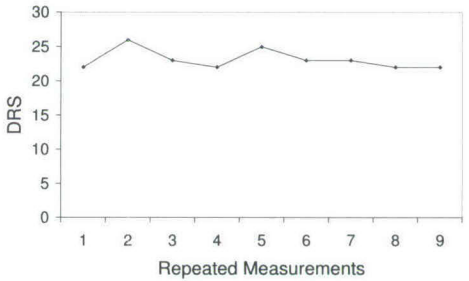
Clinical presentation and acute management

Patient 25 was a man who was 22 years old at the time of his injury.

He was injured in a traffic accident. He was found unconscious at the scene of the accident, where his GCS was E1M3V1. Initial CT brain scanning demonstrated a diffuse swelling of the brain, contusions left occipitally and temporally, punctual and intraventricular haemorrhages, diffuse axonal damage, atrophy, and damage to the brain stem. An intracranial pressure gauge and a ventricle drain were applied. A hydrocephaly was apparent, with expanded ventricles and temporal horn. Patient 25 spent 26 days at the ICU, and was transferred to the RCL 71 days after his injury (11 days after registration to the EINP).



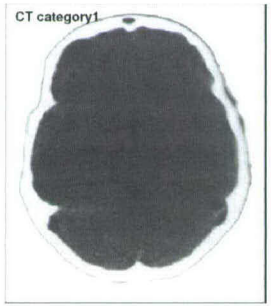




Rehabilitation programme and progress

Initially, patient 25 showed a very high muscle tension, which was displayed by chewing movements, gnashing of the teeth, and many spontaneous body movements. An increase in muscle tone occurred as a response to environmental stimulation. No directional responses were given. Although this agitation lessened, little progress was shown.

He was discharged 105 days after admission to the EINP, indicated for a nursing home.

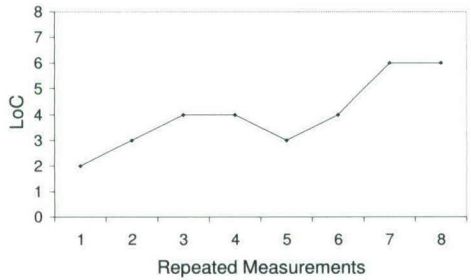


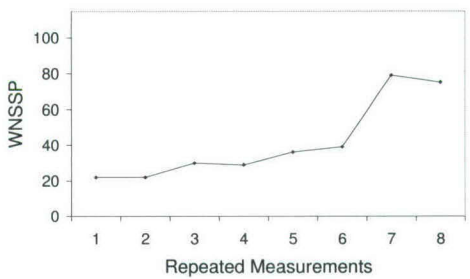
Clinical presentation and acute management

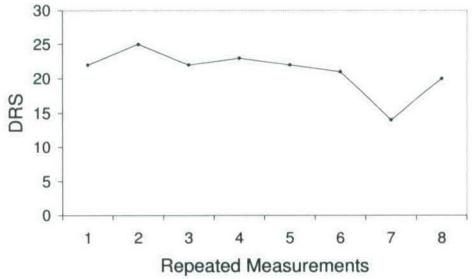
Patient 26 was a girl who was 16 years old at the time of her injury.

She was injured in a traffic accident. She was found unconscious at the scene of the accident, transferred to hospital and admitted to the intensive care unit, where her GCS was E1M2V1. Initial CT brain scanning demonstrated oedema, multiple contusions, a right subarachoid haemorrhage, and damage to the brain stem. An intracranial pressure gauge and an endotracheal tube were applied. A later CT scan showed some ischemia. There were fractures to the left femur and left mandible.

Patient 26 spent 30 days at the ICU. Patient 26 was transferred to the RCL 60 days after her injury (8 days after registration to the EINP).







Rehabilitation programme and progress

Initially, patient 26 responded to all the stimulations, in particular to the touch and pain stimulation. However, when stimulated for longer periods she was no longer motivated, and she would bend her head forward.

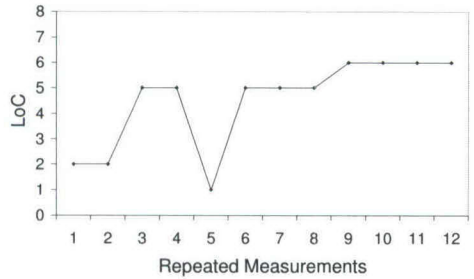
Later she started to perform tasks and respond to commands. She started to show a yes/no response. However, her acts were inconsistent. She learned to communicate using a talking computer, and she learned to read.

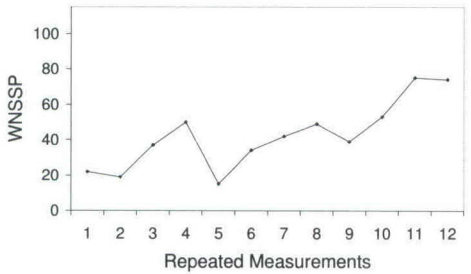
She was discharged 99 days after admission to the EINP, indicated for regular rehabilitation.

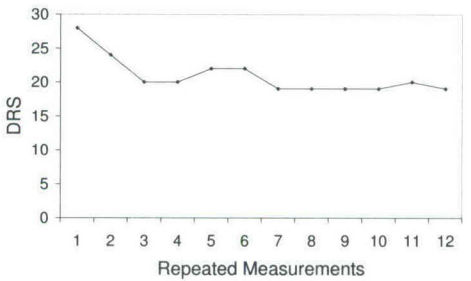
Clinical presentation and acute management

Patient 27 was a boy of 17 years old at the time of his injury.

He was injured in a traffic accident, hit by a bus while riding a bike. He was found unconscious at the scene of the accident, transferred to hospital and admitted to the intensive care unit, where his GCS was E1M1V1. Initial CT brain scanning demonstrated intraventricular haemorrhages, multiple contusions, and oedema. A later MRI showed haemorrhages in the right basal ganglia, as well as mesencephalic ischemia. His GCS minimally progressed to E2M4Vt, and he suffered pneumonia. Patient 27 spent 12 days at the ICU, and was transferred to the RCL 80 days after his injury (62 days after registration to the EINP).





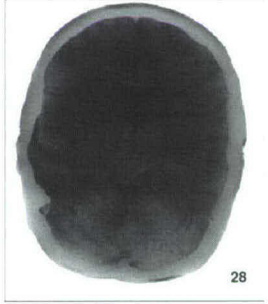


Rehabilitation programme and progress

Initially, patient 27 responded to touch and visual stimulation. His reactions were mainly movements of the arms and the legs, an increase in muscle tone, chewing movements, and turning with his head. There were extreme oscillations within his level of consciousness during the stimulation periods. It was often very difficult to arouse him. When he was awake he was able to shake a hand, and to grab objects.

Later he started the cognitive stimulation programme. He was able to perform simple functional actions. He could give a yes/no response by raising his thumb, or pushing a button, however, this was not consistent. Despite his progress, it was difficult to keep him awake. Further progress failed to occur within this period.

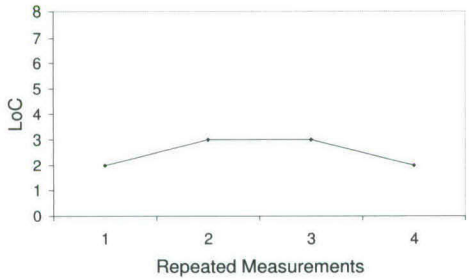
He was discharged 157 days after admission to EINP, indicated for a nursing home.

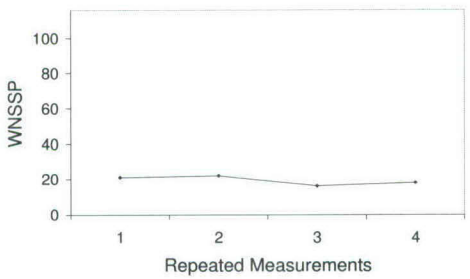


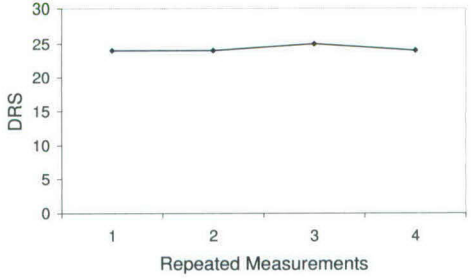
Clinical presentation and acute management

Patient 28 was a girl of 14 years old at the time of her injury.

She suffered bilateral pneumonia with a septic shock after anorexia nervosa. She was transferred to the intensive care where her GCS was E2M1V1. CT brain scanning demonstrated cortical hypodensities, and hypodensities in the basal ganglia, cortical and cerebellar atrophy, and diffuse white matter lesions. Patient 28 spent 57 days at the ICU. Patient 28 was transferred to the RCL 102 days after the injury (11 days after registration to the EINP).







Rehabilitation programme and progress

Patient 28 did not show any reaction, and did not progress during an observation period.

She was discharged 45 days after admission to the EINP, indicated for a nursing home.

Table Summary of patients' details

Ptn	Gender	Age	Cause	GCS	T1	T2	T3	T4	CT scan features*	CT category	LoC 1	LoC 2	DRS cat	GOSE	T4
1	F	25;0	Traffic accident	4	14	40	1	62	Punctual haemorrhages, focal lesions (frontal), diffuse swelling, compressed basilar cisterns	2	6	8	6	5	4,6
2	M	23;1	Explosion: blow to the head	5	28	64	18	78	Skull fracture, punctual haemorrhages, contusion (left temporal), high intracranial pressure, diffuse axonal injury	.	6	7	7	5	4,6
3	M	19;9	Traffic accident	2t	60	62	7	126	Diffuse punctual haemorrhages also in brain stem, diffuse axonal injury, diffuse white matter lesion	2	4	7	6	4	4,4
4	M	24;1	Traffic accident	6	16	42	11	76	Oedema right parietal and right and left parietofrontal, atrophy	.	2	7	7	5	4,3
5	M	17;1	Traffic accident	4t	25	40	14	71	Intraventricular haemorrhage, contusions mesencephalon, diffuse swelling, compressed basilar cisterns, atrophy	2	3	7	6	5	4,2
6	M	20;1	Traffic accident	8	23	69	5	133	Skull fracture, punctual haemorrhages, diffuse axonal injury, focal lesions and diffuse white matter lesion	.	2	7	6	3	4,3
7	M	17;7	Traffic accident	7	20	39	12	195	Skull fracture, hypoxia, punctual haemorrhages, diffuse axonal injury, contusions left parietal, right temporal and right frontal, diffuse white matter lesion	3	2	8	5	3	4,1
8	M	18;7	Traffic accident	5	11	31	14	182	Skull fracture, oedema, multiple punctual haemorrhages and contusions, diffuse swelling, diffuse white matter lesion	2	2	5	4	3	4,0
9	M	25;0	Traffic accident	6	16	38	12	80	Skull fracture punctual and subarachnoid haemorrhage, contusions right occipital, diffuse swelling	2	2	8	6	5	4,0

Ptn = Patient; F = Female; M = Male; Age = Age at injury in years; GCS = Glasgow Coma Scale at admission hospital; T1 = Time at ICU in days; T2 = Time before admission EINP in days; T3 = Time between registration and admission EINP in days; T4 = Program duration RCL in days; *diagnoses based on the medical report in the acute phase; LoC 1 = Level of Consciousness first measurement; LoC 2 = Level of Consciousness end of EINP; DRS = Disability Rating Scale; GOSE = Glasgow Outcome Scale extended; T4 = time of outcome after injury in years

Ptn	Gender	Age	Cause	GCS	T1	T2	T3	T4	CT scan features*	CT category	LoC 1	LoC 2	DRS cat	GOSE	T4
10	M	25;7	Traffic accident	2t	26	59	14	118	Skull fracture, punctual haemorrhages and intraventricular, multiple contusions	2	6	7	5	3	3,7
11	M	24;1	Traffic accident	7	58	198	111	77	Skull fracture, oedema and subarachnoid haemorrhage, multiple contusions, atrophy	.	1	2	1	1	4,1
12	M	21;3	Traffic accident	2t	57	57	21	119	Skull fracture, anoxia, oedema, and multiple contusions, diffuse swelling, high intracranial pressure	3	5	7	6	4	3,4
13	F	18;1	Traffic accident	4	32	122	19	108	Oedema, punctual and subarachnoid haemorrhages, diffuse contusions, diffuse swelling, high intracranial, pressure diffuse white matter lesions, atrophy	.	2	2	4	3	3,8
14	M	21;1	Traffic accident	5	17	79	53	34	Skull fracture, oedema, punctual and intraventricular haemorrhages, multiple contusions, ischemia, diffuse swelling, high intracranial pressure	2	5	8	6	5	3,6
15	M	17;7	Traffic accident	6	21	73	34	120	Skull fracture, multiple contusions and punctual haemorrhages, diffuse swelling	2	5	7	5	3	3,5
16	M	25;1	Traffic accident	2t	16	81	55	111	Skull fracture, left parietal and right frontal subdural haematoma, intracranial pressure, atrophy	4	3	2	1	1	3,4
17	M	17,6	Traffic accident	2t	72	80	28	139	Epidural haematoma (right), punctual haemorrhages, diffuse white matter lesions	3	3	4	3	3	3,0
18	M	6,0	Near drowning	3	8	56	28	83	Anoxia, diffuse white matter lesions, cortical frontal and tempooccipital, thalamus bilateral	.	3	8			

Ptn = Patient; F = Female; M = Male; Age = Age at injury in years; GCS = Glasgow Coma Scale at admission hospital; T1 = Time at ICU in days; T2 = Time before admission EINP in days; T3 = Time between registration and admission EINP in days; T4 = Program duration RCL in days; *diagnoses based on the medical report in the acute phase; LoC 1 = Level of Consciousness first measurement; LoC 2 = Level of Consciousness end of EINP; DRS = Disability Rating Scale; GOSE = Glasgow Outcome Scale extended; T4 = time of outcome after injury in years

Ptn	Gender	Age	Cause	GCS	T1	T2	T3	T4	CT scan features*	CT category	LoC 1	LoC 2	DRS cat	GOSE	T4
19	M	20,8	Traffic accident	4	35	60	13	105	Skull fracture, Intracerebral haemorrhages, atrophy, hypodensity, diffuse white matter lesions, puntucal haemorrhages subcortical left and right, brain stem	3	1	4	1	1	3,0
20	M	15,4	Traffic accident	4	33	136	68	112	Skull fractures, arachnoid haemorrhages, contusion and punctual haemorrhages (right frontal, temporal, parietal), diffuse swelling	3	2	5	4	3	2,9
21	M	25,2	Traffic accident	4	64	64	34	77	Skull fracture, oedema and punctual haemorrhages (cortical), diffuse swelling, and diffuse white matter lesions	3	2	8	6	3	2,7
22	M	8,4	cerebral haemorrhages	2t	33	81	52	119	Intraventricular and intracerebral haemorrhages, left cortical	.	3	7	7	3	2,6
23	F	18,8	Traffic accident	2t	29	49	7	115	Oedema, ischemia, high intracranial pressure, diffuse swelling	2	4	8	4	3	2,4
24	M	17,5	Traffic accident	4	13	44	21	92	Oedema, intraventricular and intracerebral haemorrhages, focal lesions (subcortical, brainstem), diffuse white matter lesions	2	3	8	7	6	2,5
25	M	21,8	Traffic accident	5	26	71	11	105	Punctual haemorrhages, intraventricular haemorrhage (left), diffuse swelling, diffuse axonal injury	3	2	4	3	3	2,5
26	F	15,7	Traffic accident	4	30	60	8	99	Subarachnoid haemorrhage (right), high intracranial pressure, oedema (right subcortical and brainstem)	1	2	8	5	3	2,4
27	M	17,2	Traffic accident	3	12	80	62	157	Intraventricular haemorrhages (bilateral), multiple punctual haemorrhages, Large haemorrhage in basal ganglia, and right frontal, oedema (mainly left periventricular white matter)	3	2	5	1	1	2,2

Ptn = Patient; F = Female; M = Male; Age = Age at injury in years; GCS = Glasgow Coma Scale at admission hospital; T1 = Time at ICU in days; T2 = Time before admission EINP in days; T3 = Time between registration and admission EINP in days; T4 = Program duration RCL in days; *diagnoses based on the medical report in the acute phase; LoC 1 = Level of Consciousness first measurement; LoC 2 = Level of Consciousness end of EINP; DRS = Disability Rating Scale; GOSE = Glasgow Outcome Scale extended; T4 = time of outcome after injury in years

Ptn	Gender	Age	Cause	GCS	T1	T2	T3	T4	CT scan features*	CT category	LoC 1	LoC 2	DRS cat	GOSE	T4
28	F	15,2	Pneumonia + sepsis	3	57	102	11	45	Hypodensity in basal ganglia and cortical temporoparietal, anoxia, cortical and cerebellar atrophy, diffuse white matter lesion	.	2	3			

Ptn = Patient; F = Female; M = Male; Age = Age at injury in years; GCS = Glasgow Coma Scale at admission hospital; T1 = Time at ICU in days; T2 = Time before admission EINP in days; T3 = Time between registration and admission EINP in days; T4 = Program duration RCL in days; *diagnoses based on the medical report in the acute phase; LoC 1 = Level of Consciousness first measurement; LoC 2 = Level of Consciousness end of EINP; DRS = Disability Rating Scale; GOSE = Glasgow Outcome Scale extended; T4 = time of outcome after injury in years

Dankwoord (Acknowledgements)

Dit proefschrift had niet bestaan in zijn huidige vorm, zonder hulp en supervisie.
Natuurlijk wil ik hier graag een aantal mensen bij naam en daad noemen. De volgorde waarin ik dat doe heeft geen andere betekenis dan de chronologische volgorde waarin deze mensen mijn pad hebben gekruist in de periode van mijn AIO-schap. Dit geldt niet voor familie en vrienden, die worden normaliter altijd als laatste genoemd, terwijl zij natuurlijk al eerder mijn pad hadden gekruist.

Mijn eerste dank gaat uit naar Geert van Boxtel, die mij zo'n zes jaar geleden informeerde over dit onderzoek. In het revalidatiecentrum Leijpark werd iemand gezocht die onderzoek wilde doen binnen de behandeling voor vegetatieve en minimaal bewuste patiënten, inmiddels genaamd 'Vroege Intensieve Neurorevalidatie (VIN). Als net afgestudeerde psycholoog was ik hierdoor zeer vereerd! Geert wil ik bedanken voor het vertrouwen wat hij in me moet hebben gehad om mij voor dit project te vragen.

Al snel daarna volgde mijn eerste ontmoeting met Henk Eilander, én met zijn enthousiasme en passie voor het onderwerp van het onderzoek naar VIN. Nog geen maand later begon ik met het onderzoek beschreven in dit proefschrift. Ik wil Henk bedanken voor de kans die hij me heeft gegeven om, samen met hem, onderzoek te verrichten naar de behandeling van zo'n bijzondere patiëntengroep.

Deze mensen, de patiëntengroep, wil ik bedanken voor de grootste bijdrage aan dit proefschrift: het is *jullie* neurofysiologische reactiviteit die is beschreven in dit proefschrift. Jullie zijn ook een rijke bijdrage geweest in mijn leven. Jullie moed, de stappen die jullie maakten in jullie herstel en de blijheid die jullie daarbij lieten zien, zijn voor mij een grote motivatie geweest.

Ook wil ik de familie en partners van de patiënten bedanken. Er was bijna altijd een grote bereidwilligheid om hun familielid of partner aan dit onderzoek mee te laten doen. En dat terwijl jullie in een nare en stressvolle situatie verkeerden. Voor jullie moed en positieve instelling heb ik veel bewondering.

Het zal mij ook altijd bijblijven dat de positieve sfeer op de afdeling me verbaasde. Zoals nu mijn omgeving reageert op het onderzoek wat ik verricht heb: 'Dat moet wel moeilijk zijn geweest met een dergelijke patiëntengroep', zo dacht ik ook te gaan reageren. Maar niks van dat alles. De warme, positieve en huislijke sfeer die ik aantrof op het moment waarop ik de afdeling betrad was verbazingwekkend.

Dit brengt mij bij de volgende mensen die ik wil bedanken: Het behandelteam! De manier waarop jullie deze behandeling uitvoeren is zeer te bewonderen. De manier waarop patiënten, én hun familie en partners 'onder jullie hoede' mogen zijn in deze moeilijke periode in hun leven is bewonderenswaardig.

Zo begon het dus....
Nu het onderzoek zelf....

In 2001 begonnen we een onderzoek waarvan een deel in dit proefschrift is beschreven. Ik had het geluk in te kunnen springen in deze periode. Tientallen jaren waren inmiddels verstreken, waarin Henk tijd en middelen zocht om het behandelprogramma op een wetenschappelijk verantwoorde manier te onderzoeken, en het nut ervan aan te tonen. Veel denkwerk was al verricht, en samen met Debby van Es heb je bedacht dat het meten van verschillende neurofysiologische reacties op een verscheidenheid van omgevingsstimuli, in deze patiëntengroep wel eens van groot nut zou kunnen zijn! Ik ben erg blij dat ik aan dit laatste onderdeel inhoud heb mogen geven.

Samen met Yvonne en Sylvia, mijn eerste stagiaires, ben ik begonnen met het meten van hartslag en huidgeleiding. Het is fijn om in zo'n opstartperiode zulke fanatieke stagiaires te mogen begeleiden. Ik wil jullie bedanken voor deze samenwerking. Jullie kenden de patiënten alvorens ik met hen ging werken. Met plezier denk ik terug aan het inplannen en meten van de controlegroep: kinderen van een regionale basis- en middelbare school. Zelfs in de avonduren waren we nog bezig. En iedereen kreeg een klein presentje voor de deelname: een waardebon van de wereldwinkel en een stressballetje in de vorm van hersenen.

Inmiddels waren de contacten met SPITs gelegd. De meetopstelling voor hartslag en huidgeleiding draaide overuren en het was tijd om eens naar de data te gaan kijken. Ik wil hierbij de afdeling SPITs bedanken voor alle technische ondersteuning. Met name wil ik Charles Rambelje en Ton Aalbers bedanken. Met hen heb ik, met veel plezier, intensief samengewerkt. Jullie waren altijd bereid mee te denken bij het ontwerpen van experimenten en bij het bekijken en verwerken van de gevonden data.

Mijn eerste blikken op de fysiologische data deden mij ietwat huiveren. In mijn zoektocht naar methoden om in deze patiëntengroep fysiologische reactiviteit te analyseren en interpreteren heb ik daarom ook hulp gezocht op de universiteit. Ik kwam toen uit bij Geert van Boxtel en Bea de Gelder. Ik wil hen bedanken voor het optreden als copromotor en promotor bij mijn PhD project. Ik was erg blij dat Geert mij in dit project heeft willen begeleiden. We hebben samen gezocht naar de optimale methoden om deze data te analyseren. Er zijn ontzettend veel data verzameld, waarvan een gedeelte nog wacht op analyse.

Bea offered me the opportunity to meet and discuss our findings with Prof. dr. J.M. Guérit. I want to thank Bea for introducing me to Prof. dr. J.M. Guérit. I am grateful that Prof. dr. J.M. Guérit wanted to share his knowledge on these patients and on the analyses of their neurophysiological reactivity.

Het analyseren is één ding, het opschrijven van de bevindingen is een tweede. Ik wil Geert en Bea bedanken voor hun kritische begeleiding van mijn schrijfpraktijken. Het was een hele kunst om onze ingewikkelde bevindingen en mijn gedachten hierover op een heldere en begrijpelijke manier te verwoorden.

Ook wil ik hierbij de begeleidingscommissie bedanken voor hun hulp en adviezen: dhr. H. van Dall, dr. P.L. Hoenderdaal, dr. J.C.M. Lavrijsen, dr. A.I.R. Maas, Prof. dr. A.J.H. Prevo, dr. H. Stroink, Prof. dr. A.J.J.M. Vingerhoets and Prof. dr. H. van der Vlugt.

Gedurende mijn onderzoek heb ik nog vele stagiaires mogen begeleiden. Zoals bijvoorbeeld Wim en Eef, zij kwamen bij me op het moment dat we net de nieuwe EEG-meetapparatuur ontvingen. Een hectisch moment, waarin jullie een flinke steen hebben bijgedragen. Ook Marijn heeft mee mogen proeven van de neurofysiologie! Sommige stagiaires bleven (even) hangen in het 'onderzoeksteam'. Bijvoorbeeld Susan, die nog een tijdje bij ons is gebleven om administratief werk te verrichten. En natuurlijk Matagne, die nog een heel onderzoek heeft uitgevoerd met Henk, na haar afstudeeronderzoek bij mij. Ik wil alle stagiaires bedanken voor hun hulp en voor een hele leuke tijd samen.

De samenwerking met de Universiteit van Tilburg (UVT) heb ik altijd erg plezierig gevonden. Ook al was ik een externe promovenda (buiten-AIO) ik voelde me altijd erg thuis. Ik wil Ton Heinen bedanken voor deze mogelijkheid.

Op de een of andere manier ben ik wel altijd een derde persoon in een kamer geweest, maar heb me nooit een vijfde wiel aan een wagen gevoeld. Mijn eerste kamer op de UVT heb ik gedeeld met Marius en Seger, die ik wil bedanken voor een gezellige tijd. Ook al raakten onze onderzoeksonderwerpen elkaar minimaal, onze levensvragen en -interesses raakten elkaar optimaal.

Later deelde ik een kamer met Wim, en nog iets later met Wim en Ruthger. Ook hen wil ik bedanken voor een hele gezellig tijd! Onze onderzoeksonderwerpen raakten elkaar redelijk, en ook onze levensvragen en –interesses konden wij optimaal met elkaar delen.

Niet alleen de mensen met wie ik een kamer heb gedeeld, maar ook met andere collegae heb ik een erg leuke tijd gehad, en nog steeds! Marijke, Maike and Yaniv (but also Wim, Ruthger and Seger again), thanks for the great times we spent together. I hope we will carry on these dinner-evenings together.

Verder wil ik Ilja, Jeroen, Hanneke, Karen, Jan, Sabine, Mirjam, Corné, Martijn, en alle andere (AIO)-collegae die mijn pad hebben gekruist in de periode dat ik rondliep op de UVT, erg bedanken voor de leuke, gezellige, wetenschappelijk inzichtelijke momenten die we hebben gedeeld.

Zoals ik al eerder vermelde worden familieleden en vrienden altijd als laatste genoemd. Mensen, de klus is geklaard! Voor jullie ligt dan eindelijk dat boekje wat de laatste jaren toch wel een heel groot gedeelte van mijn leven, en daarmee wellicht ook dat van jullie, heeft beheerst. De laatste 14 maanden heeft het proefschrift echter moeten concurreren met het kleine wondertje genaamd Fenna.....
Ik wil jullie allemaal bedanken!

Viona Wijnen

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Curriculum Vitae

Viona Wijnen was born on the 11th of January, 1973 in Etten-Leur, The Netherlands. After highschool she started working at the personal banking department of the ABN AMRO Bank. In 1995 she started studying Psychology in Tilburg, and obtained a master's degree in health psychology. After her graduation she worked as a research collaborator at the department of health psychology for eight months. During this period she also started her PhD research at the Rehabilitation Centre Leijpark, in collaboration with the Tilburg University.
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