Coma and Disorders of Consciousness

Second Edition

Caroline Schnakers
Steven Laureys
Editors

Springer

Coma and Disorders of Consciousness

Caroline Schnakers • Steven Laureys
Editors

Coma and Disorders of Consciousness

Second Edition

Springer

Editors
Caroline Schnakers
Department of Research
Casa Colina Hospital and
Centers for Healthcare
Pomona, CA
USA

Department of Neurosurgery
University of California
Los Angeles, CA
USA

Steven Laureys
GIGA Consciousness
Coma Science Group &
Neurology Department
Liège
Belgium

University and University
Hospital of Liège
Liège
Belgium

ISBN 978-3-319-55963-6 ISBN 978-3-319-55964-3 (eBook)
DOI 10.1007/978-3-319-55964-3

Library of Congress Control Number: 2017946341

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

To medical teams and families we see every day and who inspire us.

Foreword I

Consciousness is synonymous with human existence. Rene Descartes' bold proclamation, "Cogito ergo sum" (I think therefore I am), elegantly captures this premise. The clear inference here is that self-doubt about one's own existence establishes proof of one's existence. We exist because we know we exist. But how does one come to know that someone else is aware of his existence? Without direct access to knowledge of the self, it is impossible to prove (or disprove) the awareness of another. In normal consciousness, this problem is obviated by the multitude of behavioral expressions of conscious awareness manifested by living beings nearly every waking moment. Words, gestures, and actions, the "stuff" of consciousness, provide compelling evidence of the inner life of another. A small but significant percentage (5–10%) of those who sustain severe acquired brain injury experience prolonged disturbance in consciousness. Most will eventually recover at least basic capacity for self and environmental awareness, but this may not occur for many months and, in some cases, years. During this period of severely altered consciousness, one's existence may be stripped of the usual harbingers of an active inner life. Sensory, motor, language, perceptual, and drive systems may all be compromised in the aftermath of severe brain injury. Consequently, the repertoire of behaviors available to signal retention of conscious awareness may be dramatically narrowed or lost altogether. This predicament presents one of humankind's greatest existential dilemmas—is consciousness lost, or simply no longer apparent? This question is at the heart of *Coma and Disorders of Consciousness* edited by Caroline Schnakers and Steven Laureys. Both researchers are responsible for many seminal papers in this rapidly advancing field. Together, they have assembled an outstanding list of authors and have compiled a comprehensive volume that aptly depicts the state of the science in assessment and treatment of patients with disorders of consciousness (DOC). The book opens with a discussion of the complexities involved in behavioral approaches to assessment. Despite the challenges outlined, behavioral methods remain the "gold standard" in diagnostic assessment. The second chapter on prognosis reviews recently published long-term outcome studies, which have shed new light on the potential for meaningful late recovery potential in a substantial minority of persons with DOC. The next three chapters review novel functional

neuroimaging and electrophysiologic approaches to assessment designed primarily to identify neurophysiologic signatures of consciousness in persons who lack behavioral expressions of self or environmental awareness. The issue of caregiver burden is explored in chapter six from a multidimensional perspective that considers the interpersonal and subjective impact of long-term caretaking. There are three chapters dedicated to the ubiquitous secondary sequelae of severe brain injury: spasticity, swallowing disorders, and sleep disturbance. The authors describe the neural systems underpinning these disorders and thoughtfully discuss their relation to impaired consciousness. Chapters 10–12 provide a review of treatments that aim to promote recovery by stimulating preserved brain circuitry. Interventions range from relatively low-cost, readily accessible procedures such as sensory stimulation and off-label drugs to highly specialized noninvasive and invasive electrical stimulation techniques. The book concludes with a provocative look at ethical dilemmas, states of consciousness associated with near-death experiences, and, finally, the future of coma science. Readers of *Coma and Disorders of Consciousness* will come away with a wealth of new knowledge about the science of consciousness and a profound sense of wonder in its majesty.

Joseph T. Giacino
Harvard Medical School
Boston, MA, USA

Foreword II

During the last 30 years, I have had the opportunity to observe the evolution of knowledge as related to assessment and management of persons with disorders of consciousness (DOC). There has been much written, much debated, and much learned during that period of time. The neuroscientific understanding of DOC has matured significantly from basing opinions predominantly on neurological dogma to having evidence-based data in many areas to guide recommendations germane to assessment, prognosis, and treatment of this challenging population of patients.

As someone who had the pleasure of working with both Drs. Laureys and Schnakers, I was honored to be asked to write a foreword for *Coma and Disorders of Consciousness*, a timely and important contribution to the medical literature in this challenging area of medicine. The neurological spectrum that is subsumed under DOC is diverse, complex, and mystifying—this has served as a nidus for many researchers to attempt to define, explore, and better understand the nature of this condition, the essence of which is rooted in the concept of consciousness. But what truly defines consciousness in terms of the degree or breadth of conscious awareness in a given individual? Must conscious awareness include both awareness of self and environment? Should we assume someone is unaware because either we cannot show that they are aware or because they cannot tell us they are aware? How should our ability to prognosticate outcomes impact on clinical service provision including withdrawal or withholding of care if such is being considered? How should pain be assessed and treated in such individuals and what mechanisms are responsible for and differentially delineate the perception of pain versus the more complex phenomenon of suffering? Should the idea of treating someone to allow them to potentially become somewhat more aware be a worthwhile outcome if they were to remain severely disabled and dependent on others for care? This volume will help those engaged with this patient population, such as the treating clinician, family member, or advocate, to explore and stimulate improved practice and to further research in this area of neuroscience.

The text is unique and timely on many fronts, but most importantly it provides hope where often none may have existed and awareness of advances where many would have dismissed the potential for same. The clear message of this text is that

although the controversies associated with DOC remain partially shrouded in mystery, we are emerging into an era of better understanding that ultimately will positively impact clinical care and decision making.

Nathan D. Zasler, M.D., F.A.A.P.M&R., F.A.C.R.M.
Concussion Care Centre of Virginia, Ltd., Richmond, VA, USA
Tree of Life Services, Inc., Richmond, VA, USA
Department of Physical Medicine and Rehabilitation
Virginia Commonwealth University
Richmond, VA, USA
Department of Physical Medicine and Rehabilitation
University of Virginia, Charlottesville, VA, USA
IBIA, London, UK

Preface

Consciousness is a word worn smooth by a million tongues. Depending upon the figure of speech chosen it is a state of being, a substance, a process, a place, an epiphenomenon, an emergent aspect of matter, or the only true reality.

George Armitage Miller

Fifty years ago, the field of disorders of consciousness was a very limited field of research. Severely brain-injured patients, who are most likely to present impaired consciousness during recovery, often died. In the 1950s, the introduction of artificial breathing changed everything. The life of these patients could be extended even in cases of severe lesions to brain areas supporting the control of vital functions. The clinician started to face patients who were alive but not reactive to their surroundings. In this context, a new field was called to emerge, the disorders of consciousness. In the 1960s, Plum and Posner defined for the first time a clinical entity called the coma. Slightly later, Jennett and Teasdale developed the well-known Glasgow Coma Scale for assessing the progress of comatose patients in intensive care units. The 1980s was characterized by the development of a new kind of treatment, the sensory stimulation programs. Finally, in the late 1990s, the emergence of neuroimaging techniques opened new opportunities to study brain reactivity in patients with severe brain injuries.

However, in spite of the medical advances and the increasing number of severely brain-injured patients, the assessment and treatment of patients recovering from coma represents a very difficult and delicate task even today. The detection of signs of consciousness is complicated by the frequent motor and cognitive limitations of these patients. Treatment options are nearly absent, leaving the clinician often with a situation of palliative rather than restorative care. Even in an experimental setting, the study of patients in a coma or related disorders of consciousness is a real challenge. These patients are easily exhausted, limiting the assessment window, and spontaneous motor reactions have to be controlled for. The development of a research environment adapted to the scientific investigation of these patients is time consuming and requests important clinical and scientific expertise. For over two decades, international research teams have been working on the scientific exploration

of disorders of consciousness, with both scientific and clinical research agendas. These research teams, bridging various medical (neurology, neurosurgery, intensive care, anesthesia, physical medicine, otorhinolaryngology) and paramedical disciplines (psychology, speech therapy, physical therapy) as well as engineering and biological disciplines, have been a major player in the development of new assessment, communication, and treatment techniques for disorders of consciousness at both behavioral and neuroimaging levels. Gathering an international crowd of experts, this version should offer readers an overview of the most recent advancements in this domain.

By focusing on both clinicians and researchers as potential readers of this book, we decided to include well-established findings about diagnostic/prognostic criteria, ethical issues, assessment techniques (i.e., behavioral scales, electrophysiological explorations, and structural/functional neuroimaging), and treatment procedures, but also techniques under development (i.e., neuromodulation) which, we hope, will stimulate ideas for future research.

In conclusion, we hope to have reached our aim by offering a comprehensive and reader-friendly book to readers both familiar or not with the difficult but intriguing field of disorders of consciousness.

We hope you enjoy reading this book.

Caroline Schnakers
University of California
Los Angeles
CA, USA
Casa Colina Hospital and Centers for Healthcare
Pomona, CA, USA

Steven Laureys
University of Liege
Liege, Belgium

Contents

Contributors

Ingrid Breuskin, M.D., Ph.D. Head and Neck Carcinologic Department, Gustave Roussy, University Paris-Saclay, Villejuif, France

Helena Cassol Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium

Vanessa Charland-Verville, Ph.D. Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium

C. Chatelle Laboratory for NeuroImaging of Coma and Consciousness, Massachusetts General Hospital, Boston, MA, USA

Acute Neurorehabilitation Unit, Department of Clinical Neurosciences, University Hospital of Lausanne, Lausanne, Switzerland

Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium

Venusia Covelli Department of Psychology, e-Campus University, Milan, Italy

Julia S. Crone, Ph.D. Department of Psychology, University of California Los Angeles, Los Angeles, CA, USA

A. Demertzi, Ph.D. PICNIC Lab, Institut du Cerveau et de la Moelle Epinière (ICM), Paris, France

Brain and Spine Insititute, Hôpital Pitié-Salpêtrière, Paris, France

Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium

Haibo Di, Ph.D. Physiology Department, International Vegetative State and Consciousness Science Institute, Hangzhou Normal University, Hangzhou, Zhejiang, China

Anna Estraneo Research Laboratory and Neurorehabilitation Unit for Disorder of Consciousness, Maugeri Clinical and Scientific Institutes, IRCCS, Telese Terme (BN), Italy

Marguerite Foidart-Dessalle, M.D. Department of Physical Medicine and Rehabilitation, University Hospital of Liege, Liege, Belgium

Laura E. González-Lara Department of Psychology, The Brain and Mind Institute, The University of Western Ontario, London, ON, Canada

Olivia Gosseries, Ph.D. Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium

Department of Psychiatry, University of Wisconsin, Madison, WI, USA

Steven Laureys, M.D., Ph.D. Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium

Matilde Leonardi SOSD Neurology, Public Health, Disability—Scientifics Directorate, Neurological Institute IRCCS C.Besta Foundation, Milan, Italy

D. Lesenfants Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium

Laboratory for Neurorestorative Technology, School of Engineering, Brown University, Providence, RI, USA

Steve Majerus, Ph.D. Department of Psychology, Cognition and Behavior, University of Liège, Liège, Belgium

Géraldine Martens, M.Sc. Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium

Charlotte Martial Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium

Audrey Maudoux, M.D., Ph.D. Oto-Rhino-Laryngology Head and Neck Surgery Department, University Hospital of Liège, Liège, Belgium

Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium

Evelyne Mélotte Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium

Physical Medicine Department, University Hospital of Liège, Liège, Belgium

Martin M. Monti, Ph.D. Department of Psychology, University of California Los Angeles, Los Angeles, CA, USA

Department of Neurosurgery, David Geffen School of Medicine at UCLA, Brain Injury Research Center (BIRC), Los Angeles, CA, USA

Q. Noirhomme Department of Cognitive Neuroscience, Maastricht University, Maastricht, The Netherlands

Brain Innovation B.V., Maastricht, The Netherlands

Cyclotron Research Centre, University of Liege, Liege, Belgium

Adrian M. Owen Department of Psychology, The Brain and Mind Institute, The University of Western Ontario, London, ON, Canada

Davide Sattin SOSD Neurology, Public Health, Disability—Scientifics Directorate, Neurological Institute IRCCS C.Besta Foundation, Milan, Italy

Manuel Schabus, Ph.D. Laboratory for Sleep, Cognition and Consciousness Research, Department of Psychology, University of Salzburg, Salzburg, Austria

Centre for Cognitive Neuroscience Salzburg (CCNS), Salzburg, Austria

Nicholas D. Schiff, M.D. Feil Family Brain and Mind Research Institute, Weill Cornell Medical College, New York, NY, USA

Caroline Schnakers, Ph.D. Department of Neurosurgery, University of California Los Angeles, Los Angeles, CA, USA

Department of Research, Casa Colina Hospital and Centers for Healthcare, Pomona, CA, USA

Aurore Thibaut, Ph.D. Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium

Spaulding Neuromodulation Center, Harvard Medical School, Boston, MA, USA

Luigi Trojano Neuropsychology Laboratory, Department of Psychology, University of Campania 'Luigi Vanvitelli', Viale Ellitti, Caserta, Italy

Audrey Vanhaudenhuyse, Ph.D. Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium

Algology and Palliative Care Department, University Hospital of Liège, Liège, Belgium

John Whyte, M.D., Ph.D. Moss Rehabilitation Research Institute and MossRehab, Elkins Park, PA, USA

Malgorzata Wislowska Laboratory for Sleep, Cognition and Consciousness Research, Department of Psychology, University of Salzburg, Salzburg, Austria

Centre for Cognitive Neuroscience Salzburg (CCNS), Salzburg, Austria

Chapter 1
Behavioral Assessment and Diagnosis of Disorders of Consciousness

Caroline Schnakers and Steve Majerus

Abstract Behavioral assessment is a critical step for the detection of signs of consciousness and, hence, for diagnosis of states of altered consciousness. However, because of the presence of compromising factors such as severe functional and cognitive impairment, accurate diagnosis is a challenging enterprise, leading to serious consequences on the patient's ongoing care but also on the patient's end of care. In this review, we will describe the behavioral characteristics of the main clinical entities through which severely brain-injured patients transit before fully recovering from coma, we will describe methods for assessing consciousness at the bedside, and we will discuss the existing tools that help clinicians formulating an accurate diagnosis.

Introduction

During these last years, there has been increasing fascination for the field of disorders of consciousness. Due to progress in intensive care, more and more severely brain-injured patients survive their initial brain insult, but many of these will go through various states of impaired consciousness. The prevalence of these patients is estimated at 46 per million in the United States, 14 per million in Great Britain [1], and 36 per million in Belgium [2]. Many patients will remain in a vegetative state for a more or less extended period of time before regaining some level of consciousness (minimally conscious state). Some of these cases have received important coverage

C. Schnakers, Ph.D. (✉)
Department of Neurosurgery, University of California Los Angeles, Los Angeles, CA, USA

Department of Research, Casa Colina Hospital and Centers for Healthcare, Pomona, CA, USA
e-mail: cschnakers@ucla.edu; cschnakers@casacolina.org

S. Majerus, Ph.D.
Department of Psychology, Cognition and Behavior, University of Liège, Boulevard du Rectorat 3 B33, 4000 Liège, Belgium
e-mail: smajerus@ulg.ac.be

C. Schnakers, S. Laureys (eds.), *Coma and Disorders of Consciousness*,
DOI 10.1007/978-3-319-55964-3_1

by the media, such as the case of Terri Schiavo (1963–2005) who stayed in a vegetative state for 15 years after a cardiac arrest or the case of Terry Wallis who emerged from a minimally conscious state 19 years (1984–2003) after a severe traumatic brain injury [3]. At the same time, prolonged hospitalization is expensive. In the United States, the costs are estimated at 600,000–1,875,000 dollars per year per patient with severe traumatic injury [4]. Questions regarding end-of-life decisions are critical here, particularly in chronic vegetative patients. In a recent European survey (n = 2475), the majority of medical and paramedical professionals (66%) agreed to withdraw life support for chronic vegetative patients, while only 28% agreed for patients in a chronic minimally conscious state. Many clinicians reported that they would not want to be life-supported if they happened themselves to be in a chronic vegetative state (82%) or if they were in a chronic minimally conscious state (67%) [5]. The social, economic, and ethical consequences associated with disorders of consciousness, and particularly the vegetative state, are huge.

The term *vegetative* indicates preserved physiological functions (cardiac, respiratory, sleep/wake cycles) without clear signs of consciousness of either the self or the environment. In a sense, the body works without the mind. One of the few ways we have to differentiate patients in a vegetative state from conscious patients is to observe their spontaneous behaviors and their reactions to stimuli occurring in their environment. This behavioral assessment requests thorough expertise on behalf of the clinician. It also depends on the physical and mental capacities (particularly, the vigilance level) of the patient at the time of assessment. Missing signs of consciousness is not a rare fact, and diagnostic errors are frequent (i.e., around 40%) [6–8]. The diagnosis is, however, crucial. It influences the way the patient's care will be oriented and the way end-of-life decisions will be considered with the patient's family. Developing valid and sensitive behavioral scales to detect the presence of signs of consciousness, even subtle, therefore, represents a real challenge.

Disorders of Consciousness

Coma

Patients who survive a severe brain injury can remain unconscious for several weeks, being neither awake nor conscious. They are in a state called coma, defined as "a pathological state marked by severe and prolonged dysfunction of vigilance and consciousness" [9] (Fig. 1.1 and Table 1.1). This state usually results either from a lesion limited to the brainstem (involving the reticular activating system) or from a global brain dysfunction (most often caused by diffuse axonal injury after traumatic brain injury). The distinguishing features of coma are the continuous absence of eye opening (spontaneously or after stimulation) and the absence of oriented or voluntary motor or verbal (including vocalization) responses. There is no evidence of visual fixation or pursuit, even after manual eye opening. This state must last at least 1 h to be differentiated from a transient state such as syncope, acute

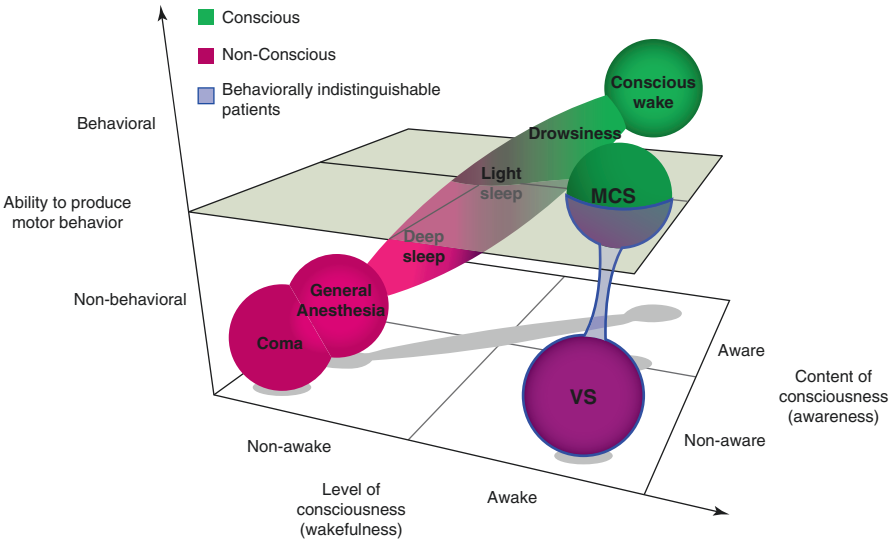

Fig. 1.1 The conundrum of consciousness. Disorders of consciousness are defined by two main components: the level of consciousness and the content of consciousness. This figure illustrates where different states (i.e., coma; vegetative state, VS; minimally conscious state, MCS, but also states related to sleep and anesthesia) are placed on both continuum. It also represents where patients with covert cognition would be placed (adapted from Monti et al., 2012)

confusion, or delirium. Prolonged coma is rare as this condition usually resolves within 2–4 weeks, most often evolving into a vegetative state or a minimally conscious state [10].

The prognosis is influenced by factors such as etiology (patients with traumatic brain injury have a better outcome than patients suffering from a cerebrovascular accident), general medical condition, and age. A negative outcome is expected if, after 3 days of observation, there are no pupillary or corneal reflexes, only stereotyped or absent motor responses to noxious stimulation, and an isoelectric electroencephalogram (EEG). A bilateral absence in parietal regions of the N20 evoked potential to somatosensory stimuli is also a strong predictor of death in comatose patients [11].

Being in a coma is different from being brain dead. In patients with brain death, critical functions such as respiration and circulation, neuroendocrine and homeostatic regulation, and consciousness are absent. The patient is apneic and unreactive to environmental stimulation. The term brain death requires a bedside demonstration of irreversible cessation of all functions of the brain, including brainstem functions. After controlling for a possible impact of pharmacological treatment, toxins, and hypothermia, the diagnosis of brain death can be made within 6–24 h, usually using a thorough assessment of brainstem reflexes, an apnea test (to demonstrate the absence of a breathing drive), and a cerebral angiography, an X-ray scan, or transcranial Doppler imaging (to demonstrate the absence of brain functions) [12].

Table 1.1 Comparison of the behavioral features of coma, VS, MCS−, MCS+, emergence from MCS (EMCS), and LIS

	Coma	VS	MCS−	MCS+	EMCS	LIS (classic)
Eye opening	None	Spontaneous	Spontaneous	Spontaneous	Spontaneous	Spontaneous
Movement	None	Reflexive/ patterned	Automatic/ object manipulation	Automatic/ object manipulation	Functional object use	Reflexive/ patterned
Response to pain	Posturing/ none	Flexion withdrawal/ posturing	Localization	Localization	N/A	Flexion withdrawal/ posturing
Visual response	None	Startle	Object localization/ pursuit/ fixation	Object recognition	Object recognition	Object recognition
Affective response	None	Random	Contingent	Contingent	Contingent	Random (presence of pathological laughs/tears)
Response to command	None	None	None	Reproducible	Consistent/ reproducible	Consistent (using eye-related commands)
Verbalization	None	None	Random vocalization/ none	Intelligible words	Intelligible words	None
Communication	None	None	Unreliable	Unreliable	Reliable	Reliable (using alphabetical board)

Vegetative State

In 1972, the term vegetative state (VS) was first introduced by Jennet and Plum to describe "an organic body capable of growth and development but devoid of sensation and thought" [13] (Fig. 1.1 and Table 1.1). This new clinical entity was identified following the implementation of artificial breathing techniques in intensive care units. Since then, the number of scientific studies performed on VS patients has continuously increased. More precisely, less than ten articles were published from 1975 to 1985, compared with more than five hundreds of articles from 2010 to 2015 (Fig. 1.2).

Behaviorally, patients in VS open their eyes spontaneously or in response to stimulation and present preserved autonomic functions (e.g., breathing, cardiovascular regulation, thermoregulation), but they are not conscious and show only reflexive behaviors [10]. The VS often results from an injury involving the white matter or bilateral lesions of the thalamus (i.e., intralaminar nuclei) [14, 15]. How can doctors explain to the family such a state? These patients breathe normally and have their eyes open. They even have prolonged periods with eyes closed, leading to the impression that the patient is sleeping. We now know that this impression may

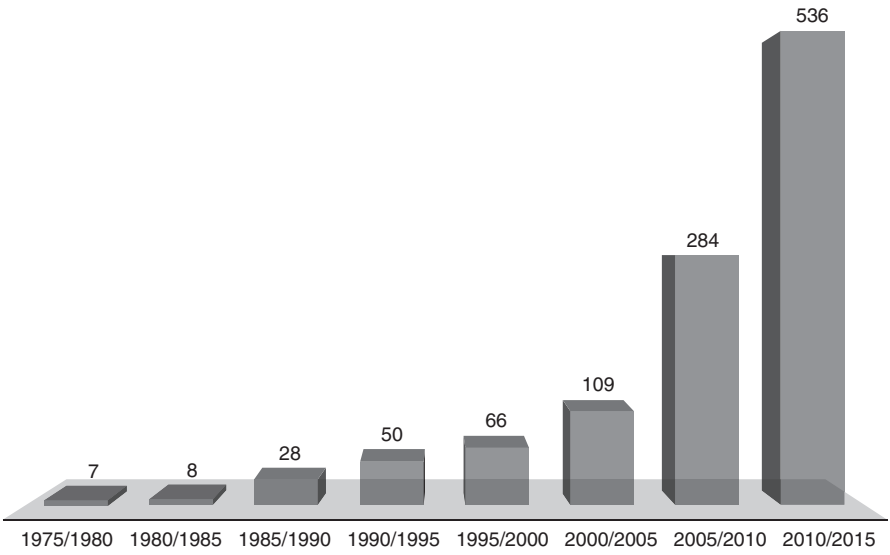

Fig. 1.2 Annual number of publications on vegetative state between 1975 and 2015. Results of a PubMed search using the terms vegetative state, consciousness, and awareness

be wrong. When the eyes are closed, no specific electroencephalographic changes are noticed, and EEG characteristics of the different sleep stages (e.g., slow wave sleep, rapid eye movement) are often absent [16]. The patients may also moan and show smiling, crying, or grimacing, but these behaviors are inappropriate and appear out of context. Even randomly produced single words have been reported in patients diagnosed with VS [17]. All of these features will puzzle the patient's family and complicate the work of the medical staff, who may be inclined to experience burnout (i.e., a recent study showed that one out of five healthcare workers caring for patients in a disorder of consciousness are in burnout, while 33% present an emotional exhaustion) [18]. Accurate information and psychological assistance are essential for helping the family (and also the medical staff) to cope with this dramatic situation [19].

The VS state may last for days, months, or even years. After 1 year, for traumatic etiologies, or 3 months, for non-traumatic etiologies, the VS can be considered as permanent. In such cases, the patient's chance of recovery is less than 5%. Only after that point can the ethical and legal issues concerning withdrawal of treatment be discussed [20]. Given the negative connotation of the term "vegetative state," the European Task Force on Disorders of Consciousness has proposed the use of a more neutral and descriptive term, such as "unresponsive wakefulness syndrome" [21]. During end-of-life decision-making, the presence of any sign of consciousness must be investigated and excluded using behavioral and neuroscientific approaches (such as neuroimaging and electrophysiology). The challenges that clinicians face when differentiating unconscious from conscious states are illustrated by cases that received lots of attention by the media such as Tony Bland in the United Kingdom

(1993), Terri Schiavo in the United States (2005), and Eluana Englaro in Italy (2009) [22–24]. Thorough examinations had been conducted for each of these patients; the extreme decision of end of life was considered. The distinction between conscious and unconscious states is very difficult to make given that patients can present subtle behavioral signs which can easily be missed and which differentiate the vegetative state from the minimally conscious state.

Minimally Conscious State

The minimally conscious state (MCS) was identified more recently than the VS and the coma. It was defined in 2002 by the Aspen Workgroup as being characterized by the presence of inconsistent but clearly discernible behavioral signs of consciousness (Fig. 1.1 and Table 1.1) [25]. Patients evolving from a VS to an MCS are still awake but begin to show oriented behaviors such as visual pursuit. The earlier this behavior appears, the better the outcome will be. The presence of oriented eye movements is therefore crucial, but it is also one of the most difficult signs of consciousness to detect and requires the use of sensitive diagnostic tools [8, 26, 27]. More globally, signs of consciousness in MCS patients may be hard to observe because they are inconsistent in time, due to high vigilance fluctuations. They must be replicated within a given examination to meet the diagnostic criteria for MCS. It is generally necessary to conduct serial examinations before an accurate diagnosis can be made. Complicating further the diagnosis is the fact that patients may fluctuate between VS and MCS before the level of consciousness stabilizes [28].

MCS is diagnosed when there is clear evidence of one or more of the following behaviors: simple command-following (e.g., “shake my hand”), gestural or verbal yes/no responses (regardless of accuracy), intelligible verbalization, and movements or affective behaviors that occur in contingent relation to relevant environmental stimuli and are not attributable to reflexive activity. Examples of contingent motor and affective responses include (1) episodes of crying, smiling, or laughter produced by the linguistic or visual content of emotional but not neutral stimuli, (2) vocalizations or gestures that occur in direct response to verbal prompts, (3) reaching for objects with a clear relationship between object location and direction of reach, (4) touching or holding objects in a manner that accommodates the size and shape of the object, and (5) visual pursuit or sustained fixation in response to moving or salient stimuli. As different functional neuroanatomical features have been observed, the MCS has recently been subdivided in two clinical entities, MCS+ and MCS−, based on the presence or absence of receptive and expressive language (i.e., response to command and intelligible verbalization) [29]. The specific behaviors required to fulfill the criteria for MCS+ and MCS− remain a matter of debate and require further empirical investigation before they can be incorporated into clinical practice.

Emergence from MCS is defined by the reemergence of reliable and consistent interactive communication (which may occur through speech, writing, yes/no signals, or augmentative communication devices) or a functional object use (i.e., discrimination and appropriate use of two or more objects) [25].

Patients in MCS may progress quickly or slowly, whereas others remain in this condition permanently. Formal prognostic guidelines do not exist for MCS. However, patients in MCS improve faster and have better prospects for functional recovery than those in VS, and outcomes are generally more favorable for those with traumatic versus non-traumatic injuries [30–32]. The original report describing this condition states that most of those who remain in MCS for 12 months will remain permanently severely disabled [33]. However, recent studies suggest that signs of recovery after severe brain injury may be observable over longer time periods and approximately one in five MCS patients will eventually continue his life at home or in the community. The duration of MCS nevertheless seems to be a strong predictor of the length of confusional state/posttraumatic amnesia [30]. The early recovery (within 8 weeks) of target conscious behaviors such as visual pursuit and response to command have been linked to good functional outcome several years after the injury [27, 31].

Don't Judge a Book by Its Cover: The Difficult Diagnoses of Locked-In Syndrome and Covert Cognition

Locked-In Syndrome

The locked-in syndrome (LIS) is marked by tetraplegia and anarthria in the context of preserved consciousness and a near-normal to normal cognitive functioning [34, 35] (Table 1.1). This state is caused by a lesion involving the ventral pons and, in 60% of cases, is due to basilar thrombosis. Functional neuroimaging typically shows preserved supratentorial areas (with hypometabolism in the cerebellum). Interestingly, significant hyperactivity has been observed bilaterally in the amygdala of acute LIS patients, likely reflecting anxiety generated by the inability to move or speak (stressing the importance of appropriate anxiety treatment soon after diagnosis) [36]. Because patients with LIS have spontaneous eyes opening, but are unable to speak or move the extremities, this state can be confused with VS. On average, the diagnosis of LIS is not established until 2.5 months post-onset. There is evidence that family members tend to detect signs of consciousness (55% of cases) prior to medical staff (23% of cases) [36]. Classic LIS consists of complete paralysis of the orobuccal musculature and all four extremities; however, vertical eye movements are spared, allowing nonverbal communication through directional gaze. Perceptual functions are also usually spared given that ascending corticospinal axons remain intact [34]. Bauer has described multiple varieties of LIS, including the incomplete form in which

there is residual motor activity (frequently, finger or head movements), and total LIS, in which there is complete immobility including both horizontal and vertical eye movements [37]. Total LIS cases have previously been reported but are rare and request the use of neuroimaging or electrophysiological methods to establish the diagnosis [38]. Data on life expectancy suggest that some patients with LIS can live for more than 12 years while remaining in LIS. Surprisingly, chronic LIS patients rate their quality of life similarly to the healthy population [39]. In the absence of other structural or functional brain abnormalities, patients with LIS are generally able to make independent decisions and communicate their preferences through augmentative communication devices [36].

Patients with Covert Cognition

A different group of patients who are unable to show any behavioral sign of consciousness but are able to respond mentally to active neuroimaging or electrophysiological paradigms has been identified more recently (Fig. 1.1). In 2006, Owen and colleagues reported the case of a non-communicative young woman with severe brain injury. When performing a mental imagery task, her brain activity was similar to the one observed in healthy controls [40]. Following this study, Monti and colleagues have tested 54 patients using the same paradigm. Only two patients diagnosed as being in a VS and three patients diagnosed as being in an MCS were able to perform the task (9% of the group). One of these patients was able to answer "yes" or "no" to autobiographical questions by using either motor or spatial imagery [41]. Since then, a series of studies has been published about the detection of willful brain activity in patients diagnosed as being in a VS, confirming the existence of patients with covert cognition [42].

It is tempting to think that these patients are with a severe form of LIS. However, unlike LIS patients, patients with covert cognition present impaired connectivity between subcortical and cortical, such as connections between the thalamus and the primary motor cortex which will prevent the execution of willful motor actions [43]. According to a recent meta-analysis, covert cognition seems rare in VS (14% of cases) but is more frequent in patients with traumatic brain injury than non-traumatic brain injury (32% vs. 19%) [42]. Future studies will nevertheless have to be multicentric in order to gather a sufficient amount of data to establish the profile of this possibly new clinical entity.

As previous findings have shown the presence of communication in some patients with covert cognition, recent studies have been trying to investigate the interest of brain-computer interfaces (BCIs) in severely brain-injured patients which may help those patients to communicate using neuroimaging or electrophysiology [41, 44–47]. BCI paradigms should not be used for diagnostic purpose. The tasks used to communicate are complex and could lead some patients

to be unable to respond even though they are conscious. Future studies will most likely have to better understand residual cognitive functioning in those patients before implementing successfully those augmentative communication techniques [48].

Bedside Assessment

Diagnostic Accuracy

Differentiating MCS from VS can be challenging as voluntary and reflexive behaviors may be difficult to distinguish and subtle signs of consciousness may be missed. The development of diagnostic criteria for MCS [25] should reduce the incidence of misdiagnosis relative to the rates reported before these criteria were established [6, 7]. However, a study comparing clinical non-standardized observation to examination with a standardized behavioral scale found that 41% of patients believed to be in VS were misdiagnosed [8]. This study also found that the majority of cases with an uncertain diagnosis were in MCS (89%), not in VS. Another 10% diagnosed with MCS based on non-standardized examination had actually emerged from this condition.

This high rate of misdiagnosis likely reflects several sources of variance. Variance in diagnostic accuracy may result from biases contributed by the examiner, patient, and environment. Examiner error may arise when the range of behaviors sampled is too narrow, response time windows are over- or under-inclusive, criteria for judging purposeful responses are poorly defined, and examinations are conducted too infrequently to capture the full range of behavioral fluctuation. The use of standardized rating scales offers some protection against these errors [32], although failure to adhere to specific administration and scoring guidelines may jeopardize diagnostic accuracy. The second source of variance concerns the patient. Fluctuations in arousal level, fatigue, subclinical seizure activity, occult illness (e.g., metabolic and infectious encephalopathies), pain, cortical sensory deficits (e.g., cortical blindness/deafness), motor impairment (e.g., generalized hypotonus, spasticity, or paralysis), or cognitive disturbance (e.g., aphasia, apraxia, agnosia) also decrease the probability of observing signs of consciousness [49]. Finally, the environment in which the patient is evaluated may bias the assessment. Paralytic and sedating medications, restricted range of movement stemming from restraints and immobilization techniques, poor positioning, and excessive ambient noise/heat/light can all decrease or distort voluntary behavioral responses.

Examiner bias can be greatly minimized by using standardized tools, but diagnostic accuracy is not always within the examiner's control. This is particularly troubling as clinical management, from rehabilitation to end-of-life decision-making, often depends on the behavioral observations of the examiner.

Behavioral Scales

In light of the behavioral fluctuations that commonly occur in this population, evaluations should be repeated over time, and measures should be sensitive enough to detect subtle but clinically meaningful changes in neurobehavioral responsiveness. Conventional bedside assessment procedures and neurosurgical rating scales such as the Glasgow Coma Scale [50] (GCS) have limited utility when used to monitor progress in patients with prolonged disturbance in consciousness. These procedures detect relatively gross changes in behavior and are not designed to distinguish random or reflexive behaviors from those that are volitional. The Full Outline of UnResponsiveness score (FOUR score) has greater sensitivity than the GCS for detecting different levels of brainstem function in the acute stage of severe brain injury [51], but because the FOUR score does not include a systematic assessment of signs of consciousness [25], it may not capture the transition from VS to MCS [52, 53]. Standardized rating scales have been devised for chronic disorders of consciousness (DOC) to address these shortcomings, to assess a broad range of neurobehavioral functions, and to rely on fixed administration and scoring procedures.

Standardized neurobehavioral assessment measures tailored for DOC patients include the Coma Recovery Scale – Revised (CRS-R) [54], the Coma-Near Coma Scale (CNC) [55], the Western Neurosensory Stimulation Profile (WNSSP) [56], the Western Head Injury Matrix (WHIM) [57], and the Sensory Modality Assessment and Rehabilitation Technique (SMART) [58]. Although item content varies across measures, all evaluate behavioral responses to a variety of auditory, visual, motor, and communication prompts. All of these instruments have been shown to have adequate reliability and validity; however, there is considerable variability in their psychometric integrity and clinical utility. Of these measures, the CRS-R is the only one that directly incorporates the existing diagnostic criteria for coma, VS, and MCS into the administration and scoring scheme (Table 1.2). Giacino and colleagues (2004) compared the CRS-R to the DRS in 80 patients with DOC and found that although the two scales produced the same diagnosis in 87% of cases, the CRS-R identified ten patients in MCS who were classified as VS on the DRS [28]. There were no cases in which the DRS detected features of MCS missed by the CRS-R. Schnakers and colleagues (2006) administered the GCS, CRS-R, and FOUR score to 60 patients with acute (i.e., trauma center) and subacute (i.e., rehabilitation center) brain injury resulting in disturbance in consciousness [52]. Among the 29 patients diagnosed with VS on the GCS, four were found to have at least one sign of consciousness on the FOUR. However, the CRS-R detected evidence of MCS in seven additional patients diagnosed with VS on the FOUR. All seven of these patients showed sustained oriented eye movements, a clinical sign heralding recovery from VS.

In 2010, the American Congress of Rehabilitation Medicine published the results of the first evidence-based review of neurobehavioral rating scales designed specifically for patients with DOC [59]. Six of the 13 scales that qualified for the review were recommended for use in clinical practice. The CRS-R received the strongest

Table 1.2 Coma Recovery Scale – Revised record sheet

Auditory function scale
4—Consistent movement to command[a]
3—Reproducible movement to command[a]
2—Localization to sound
1—Auditory startle
0—None
Visual function scale
5—Object recognition[a]
4—Object localization: reaching[a]
3—Pursuit eye movements[a]
2—Fixation[a]
1—Visual startle
0—None
Motor function scale
6—Functional object use[b]
5—Automatic motor response[a]
4—Object manipulation[a]
3—Localization to noxious stimulation[a]
2—Flexion withdrawal
1—Abnormal posturing
0—None/flaccid
Oromotor/verbal function scale
3—Intelligible verbalization[a]
2—Vocalization/oral movement
1—Oral reflexive movement
0—None
Communication scale
2—Functional: accurate[b]
1—Nonfunctional: intentional[a]
0—None
Arousal scale
3—Attention[a]
2—Eye opening without stimulation
1—Eye opening with stimulation
0—Unarousable

[a]Denotes MCS
[b]Denotes emergence from MCS

recommendation ("minor reservations"), based on its performance across a panel of psychometric quality indicators. The CRS-R is also one of the Traumatic Brain Injury (TBI) Common Data Elements (CDE) suggested by the US National Institute of Neurological Disorders and Stroke (NINDS) and the method of choice for monitoring recovery of consciousness in TBI research [60, 61].

More Specialized Behavioral Assessments

Individualized Quantitative Behavioral Assessment

Clinicians involved in the care of MCS patients often encounter situations in which the patients' behavioral responses are ambiguous or occur too infrequently to clearly discern their significance. These problems are often due to injury-related sensory, motor, and arousal deficits. For this reason, a technique referred to as Individualized Quantitative Behavioral Assessment (IQBA) was developed by Whyte and colleagues [62, 63]. IQBA is intended to address case-specific questions using individually tailored assessment procedures, operationally defined target responses, and controls for examiner and response bias. Once the target behavior (e.g., command-following, visual tracking) has been operationalized, the frequency of the behavior is recorded following administration of an appropriate command, following an incompatible command and during a rest interval. Data are analyzed statistically to determine whether the target behavior occurs significantly more often in one condition relative to other conditions. For example, when the frequency of observed behaviors is greater during the "rest" condition relative to the "command" condition, it is likely that the behaviors represent random movement rather than a purposeful response to command.

IQBA can be applied across a broad range of behaviors and can address many different types of clinical question. McMillan (1996) employed an IQBA protocol to determine whether a minimally responsive, TBI patient could reliably communicate a preference concerning withdrawal of life-sustaining treatment [64]. Responses to questions were executed using a button press. Results indicated that the number of affirmative responses to "wish to live" questions was significantly greater than chance suggesting that the patient could participate in end-of-life decision-making. McMillan's findings were subsequently replicated in a second IQBA assessment conducted by a different group of examiners [65].

Pain Assessment and the Nociception Coma Scale – Revised

Providing information as to whether a patient with DOC is in pain is important to both clinicians and families. However, self-report is not an option in patients with DOC because of the inability to communicate. The Nociception Coma Scale (NCS) is the first standardized tool developed to assess nociceptive pain in patients with severe brain injury. The first version of the NCS consisted of four subscales assessing motor, verbal, visual responses as well as facial expression [66]. The NCS has been validated in patients in intensive care and inpatient neurology/neurosurgery units, rehabilitation centers, and nursing homes. In comparison to other pain scales developed for non-communicative patients, the NCS has broader coverage and better diagnostic sensitivity, suggesting that it is an appropriate assessment tool for this

population. The visual subscale was subsequently deleted since further analysis showed that, following the application of noxious versus non-noxious stimuli, significantly higher scores were obtained on the motor, verbal, and facial expression subscales but not on the visual subscale. Using this revised version (NCS-R), a cutoff score of 4 (sensitivity of 73% and specificity of 97%) has been defined as a potential clinical threshold for detecting pain in patients with DOC [67]. Recent findings have also shown a correlation between NCS-R total scores and the activity in the anterior cingulate cortex (related to pain unpleasantness), reflecting further the relevance of this scale when monitoring pain in patients with DOC [68]. The scale has demonstrated good reliability and validity and currently exists in various languages (i.e., French, English, Italian, Dutch, and Thai) [66, 67, 69–72]. Finally, the interest of the NCS-R in assessing pain in a clinical setting has been investigated recently [73]. Thirty-nine patients with potential painful conditions (e.g., due to fractures, decubitus ulcers, or spasticity) were assessed with the NCS-R and the GCS during nursing cares before and after the administration of an analgesic treatment tailored to each patient's clinical status. The NCS-R scores, but not the GCS scores, were statistically lower during treatment when compared to the scores obtained before treatment, providing further evidence that the NCS-R is an interesting clinical tool specifically tailored for pain management.

Conclusion

Behavioral responses as well as brain activity differ among disorders of consciousness. The detection of signs of consciousness can be challenging at the bedside and the use of sensitive standardized scales is crucial. As misdiagnosis can lead to serious consequences especially in terms of pain treatment and end-of-life decision-making, neuroimaging could constitute a complementary tool when disentangling VS from MCS patients. In the future, the development of consciousness classifier based on residual brain activity or residual brain connectivity could also substantially help clinicians and constitute an automated diagnostic tool. This could particularly help for the detection of patients who are functionally locked-in.

References

1. Jennett B. 30 Years of the vegetative state: clinical, ethical and legal problems. In: Laureys S, editor. The boundaries of consciousness: neurobiology and neuropathology, vol. 150. Amsterdam: Elsevier; 2005. p. 541–8.
2. Demotte R. Politique de la santé à mener à l'égard des patients en état végétatif persistant ou en état pauci-relationnel. Moniteur Belge. 2004;69:334–40.
3. Wijdicks EF. Minimally conscious state vs. persistent vegetative state: the case of Terry (Wallis) vs. the case of Terri (Schiavo). Mayo Clin Proc. 2006;81(9):1155–8.

4. Consensus Conference. Rehabilitation of persons with traumatic brain injury. NIH consensus development panel on rehabilitation of persons with traumatic brain injury. JAMA. 1999;282(10):974–83.
5. Demertzi A, Ledoux D, Bruno MA, et al. Attitudes towards end-of-life issues in disorders of consciousness: a European survey. J Neurol. 2011;258:1058–65.
6. Childs NL, Mercer WN, Childs HW. Accuracy of diagnosis of persistent vegetative state. Neurology. 1993;43(8):1465–7.
7. Andrews K, Murphy L, Munday R, Littlewood C. Misdiagnosis of the vegetative state: retrospective study in a rehabilitation unit. BMJ. 1996;313(7048):13–6.
8. Schnakers C, Vanhaudenhuyse A, Giacino J, et al. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. BMC Neurol. 2009;9:35.
9. Posner J, Saper C, Schiff N, et al. Plum and Posner's diagnosis of stupor and coma. New York: Oxford University Press; 2007.
10. The Multi-Society Task Force on Persistent Vegetative State. Medical aspects of the persistent vegetative state. N Engl J Med. 1994;330(21):1499–508.
11. Bouwes A, Binnekade JM, Kuiper MA, et al. Prognosis of coma after therapeutic hypothermia: a prospective cohort study. Ann Neurol. 2012;71(2):206–12.
12. Wijdicks EF, Varelas PN, Gronseth GS, et al., American Academy of Neurology. Evidence-based guideline update: determining brain death in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2010;74(23):1911–8.
13. Jennett B, Plum F. Persistent vegetative state after brain damage: a syndrome in search of a name. Lancet. 1972;1:734–7.
14. Fernández-Espejo D, Junque C, Bernabeu M, et al. Reductions of thalamic volume and regional shape changes in the vegetative and the minimally conscious states. J Neurotrauma. 2010;27(7):1187–93.
15. Newcombe VF, Williams GB, Scoffings D, et al. Aetiological differences in neuroanatomy of the vegetative state: insights from diffusion tensor imaging and functional implications. J Neurol Neurosurg Psychiatry. 2010;81(5):552–61.
16. Landsness E, Bruno MA, Noirhomme Q, et al. Electrophysiological correlates of behavioural changes in vigilance in vegetative state and minimally conscious state. Brain. 2011;134(8): 2222–32.
17. Working Party of the Royal College of Physicians. The vegetative state: guidance on diagnosis and management. Clin Med. 2003;3(3):249–54.
18. Gosseries O, Demertzi A, Ledoux D, et al. Burnout in healthcare workers managing chronic patients with disorders of consciousness. Brain Inj. 2012;26(12):1493–9.
19. Leonardi M, Giovannetti AM, Pagani M, et al. Burden and needs of 487 caregivers of patients in vegetative state and in minimally conscious state: results from a national study. Brain Inj. 2012;26(10):1201–10.
20. Jennett B. The assessment and rehabilitation of vegetative and minimally conscious patients: definitions, diagnosis, prevalence and ethics. Neuropsychol Rehabil. 2005;15:163–5.
21. Laureys S, Celesia GG, Cohadon F, et al. Unresponsive wakefulness syndrome: A new name for the vegetative state or apallic syndrome. BMC Med. 2010;8:68.
22. Andrews K. Medical decision making in the vegetative state: withdrawal of nutrition and hydration. NeuroRehabilitation. 2004;19:299–304.
23. Cohen NH, Kummer HB. Ethics update: lessons learned from Terri Schiavo—the importance of healthcare proxies in clinical decision-making. Curr Opin Anaesthesiol. 2006;19(2): 122–6.
24. Luchetti M. Eluana Englaro, chronicle of a death foretold: ethical considerations on the recent right-to-die case in Italy. J Med Ethics. 2010;36(6):333–5.
25. Giacino J, Ashwal S, Childs N, et al. The minimally conscious state: definition and diagnostic criteria. Neurology. 2002;58(3):349–53.
26. Candelieri A, Cortese MD, Dolce G, et al. Visual pursuit: within-day variability in the severe disorder of consciousness. J Neurotrauma. 2011;28(10):2013–7.

27. Dolce G, Lucca LF, Candelieri A, et al. Visual pursuit in the severe disorder of consciousness. J Neurotrauma. 2011;28(7):1149–54.
28. Giacino JT, Trott CT. Rehabilitative management of patients with disorders of consciousness: grand rounds. J Head Trauma Rehabil. 2004;19(3):254–65.
29. Bruno MA, Majerus S, Boly M, et al. Functional neuroanatomy underlying the clinical subcategorization of minimally conscious state patients. J Neurol. 2012;259(6):1087–98.
30. Katz DI, Polyak M, Coughlan D, et al. Natural history of recovery from brain injury after prolonged disorders of consciousness: outcome of patients admitted to inpatient rehabilitation with 1-4 year follow-up. Prog Brain Res. 2009;177:73–88.
31. Whyte J, Nakase-Richardson R, Hammond FM, et al. Functional outcomes in traumatic disorders of consciousness: 5-year outcomes from the National Institute on Disability and Rehabilitation Research Traumatic Brain Injury Model Systems. Arch Phys Med Rehabil. 2013;94(10):1855–60.
32. Estraneo A, Moretta P, Loreto V, et al. Clinical and neuropsychological long-term outcomes after late recovery of responsiveness: a case series. Arch Phys Med Rehabil. 2014;95(4):711–6.
33. Fins JJ, Schiff ND, Foley KM. Late recovery from the minimally conscious state: ethical and policy implications. Neurology. 2007;68:304–7.
34. American Congress of Rehabilitation Medicine. Recommendations for use of uniform nomenclature pertinent to persons with severe alterations in consciousness. Arch Phys Med Rehabil. 1995;76:205–9.
35. Schnakers C, Majerus S, Goldman S, et al. Cognitive function in the locked-in syndrome. J Neurol. 2008;255(3):323–30.
36. Laureys S, Pellas F, Van Eeckhout P, et al. The locked-in syndrome: what is it like to be conscious but paralyzed and voiceless? Prog Brain Res. 2005;150:495–511.
37. Bauer G, Gerstenbrand F, Rumpl E. Varieties of the locked-in syndrome. J Neurol. 1979;221(2):77–91.
38. Schnakers C, Perrin F, Schabus M, et al. Detecting consciousness in a total locked-in syndrome: an active event-related paradigm. Neurocase. 2009;15(4):271–7.
39. Bruno MA, Bernheim JL, Ledoux D, et al. A survey on self-assessed well-being in a cohort of chronic locked-in syndrome patients: happy majority, miserable minority. BMJ Open. 2011;1(1):e000039.
40. Owen AM, Coleman MR, Boly M, et al. Detecting awareness in the vegetative state. Science. 2006;313(5792):1402.
41. Monti MM, Vanhaudenhuyse A, Coleman MR, et al. Willful modulation of brain activity in disorders of consciousness. N Engl J Med. 2010;362(7):579–89.
42. Kondziella D, Friberg CK, Frokjaer VG, et al. Preserved consciousness in vegetative and minimal conscious states: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2015; pii: jnnp-2015-310958.
43. Fernández-Espejo D, Rossit S, Owen AM. A thalamocortical mechanism for the absence of overt motor behavior in covertly aware patients. JAMA Neurol. 2015;72(12):1442–50.
44. Kübler A, Furdea A, Halder S, et al. A brain-computer interface controlled auditory event-related potential (p300) spelling system for locked-inpatients. Ann N Y Acad Sci. 2009;1157:90–100.
45. Naci L, Monti MM, Cruse D, et al. Brain-computer interfaces for communication with nonresponsive patients. Ann Neurol. 2012;72(3):312–23.
46. Naci L, Owen AM. Making every word count for nonresponsive patients. JAMA Neurol. 2013;70(10):1235–41.
47. Lulé D, Noirhomme Q, Kleih SC, et al. Probing command following in patients with disorders of consciousness using a brain-computer interface. Clin Neurophysiol. 2013;124(1):101–6.
48. Schnakers C, Giacino JT, Løvstad M, et al. Preserved covert cognition in noncommunicative patients with severe brain injury? Neurorehabil Neural Repair. 2015;29(4):308–17.
49. Schnakers C, Bessou H, Rubi-Fessen I, et al. Impact of aphasia on consciousness assessment: a cross-sectional study. Neurorehabil Neural Repair. 2015;29(1):41–7.

50. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. Lancet. 1974;2:81–4.
51. Wijdicks EF, Bamlet WR, Maramattom BV, et al. Validation of a new coma scale: the FOUR score. Ann Neurol. 2005;58(4):585–93.
52. Schnakers C, Giacino J, Kalmar K, et al. Does the FOUR score correctly diagnose the vegetative and minimally conscious states? Ann Neurol. 2006;60(6):744–5.
53. Bruno MA, Ledoux D, Lambermont B, et al. Comparison of the full outline of unresponsiveness and Glasgow Liege Scale/Glasgow Coma Scale in an intensive care unit population. Neurocrit Care. 2011;15(3):447–53.
54. Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil. 2004;85(12):2020–9.
55. Rappaport M, Dougherty AM, Kelting DL. Evaluation of coma and vegetative states. Arch Phys Med Rehabil. 1992;73:628–34.
56. Ansell BJ, Keenan JE. The Western Neuro Sensory Stimulation Profile: a tool for assessing slow-to-recover head-injured patients. Arch Phys Med Rehabil. 1989;70:104–8.
57. Shiel A, Horn SA, Wilson BA, et al. The Wessex Head Injury Matrix (WHIM) main scale: a preliminary report on a scale to assess and monitor patient recovery after severe head injury. Clin Rehabil. 2000;14(4):408–16.
58. Wilson SL, Gill-Thwaites H. Early indications of emergence from vegetative state derived from assessment with the SMART—a preliminary report. Brain Inj. 2000;14(4):319–31.
59. Seel RT, Sherer M, Whyte J, et al. Assessment scales for disorders of consciousness: evidence-based recommendations for clinical practice and research. Arch Phys Med Rehabil. 2010;91(12):1795–813.
60. Hicks R, Giacino J, Harrison-Felix C, et al. Progress in developing common data elements for traumatic brain injury research: version two—the end of the beginning. J Neurotrauma. 2013;30(22):1852–61.
61. Wilde EA, Whiteneck GG, Bogner J, et al. Recommendations for the use of common outcome measures in traumatic brain injury research. Arch Phys Med Rehabil. 2010;91(11):1650–60.
62. Whyte J, DiPasquale M. Assessment of vision and visual attention in minimally responsive brain injured patients. Arch Phys Med Rehabil. 1995;76(9):804–10.
63. Whyte J, DiPasquale M, Vaccaro M. Assessment of command-following in minimally conscious brain injured patients. Arch Phys Med Rehabil. 1999;80:1–8.
64. McMillan TM. Neuropsychological assessment after extremely severe head injury in a case of life or death. Brain Inj. 1996;11(7):483–90.
65. Shiel A, Wilson B. Assessment after extremely severe head injury in a case of life or death: further support for McMillan. Brain Inj. 1998;12(10):809–16.
66. Schnakers C, Chatelle C, Vanhaudenhuyse A, et al. The Nociception Coma Scale: a new tool to assess nociception in disorders of consciousness. Pain. 2010;148(2):215–9.
67. Chatelle C, Majerus S, Whyte J, et al. A sensitive scale to assess nociceptive pain in patients with disorders of consciousness. J Neurol Neurosurg Psychiatry. 2012;83(12):1233–7.
68. Chatelle C, Thibaut A, Gosseries O, et al. Changes in cerebral metabolism in patients with a minimally conscious stat responding to zolpidem. Front Hum Neurosci. 2014;8:917.
69. Riganello F, Cortese MD, Arcuri F, et al. A study of the reliability of the Nociception Coma Scale. Clin Rehabil. 2015;29(4):388–93.
70. Sattin D, Pagani M, Covelli V, et al. The Italian version of the Nociception Coma Scale. Int J Rehabil Res. 2013;36(2):182–6.
71. Suraseranivongse S, Yuvapoositanont P, Srisakkrapikoop P, et al. A comparison of pain scales in patients with disorders of consciousness following craniotomy. J Med Assoc Thai. 2015;98(7):684–92.
72. Vink P, Eskes AM, Lindeboom R, et al. Nurses assessing pain with the Nociception Coma Scale: interrater reliability and validity. Pain Manag Nurs. 2014;15(4):881–7.
73. Chatelle C, De Val MD, Catano A, et al. Is the Nociception Coma Scale-revised a useful clinical tool for managing pain in patients with disorders of consciousness? Clin J Pain. 2016;32(4):321–6.

Chapter 2
Prognosis in Disorders of Consciousness

Anna Estraneo and Luigi Trojano

Abstract In patients with prolonged disorders of consciousness (DOC), clinical evolution is determined by several factors closely interacting with each other: etiology, patient's age (likely influencing the physiological process of recovery, e.g., brain plasticity), the duration of DOC (likely related to the severity of brain damage), the structural and functional integrity of neuronal populations (as assessed by neurophysiological and neuroimaging methods), and the presence of clinical complications that could impact care strategies.

In the present chapter, we will offer a brief review of the most recent studies on clinical evolution of patients with prolonged DOC and of the longitudinal studies searching for robust prognostic markers in such patients. We will argue that some prognostic indicators for patients in vegetative state can be gathered in the rehabilitative phase, whereas reliable markers to characterize DOC patients who will present late recovery of responsiveness and consciousness have not been identified. Moreover, long-term evolution of patients in minimally conscious state has not been clearly established, and definite prognostic information is not available for these patients. For these reasons, prospective longitudinal systematic investigations of outcome in large groups of individual with prolonged DOC are needed to better clarify the natural recovery of DOC and to define prognostic markers useful to update current positions on medical, ethical, and legal issues connected with management and care of these patients.

A. Estraneo (✉)
Research Laboratory and Neurorehabilitation Unit for Disorder of Consciousness,
Maugeri Clinical and Scientific Institutes, IRCCS,
Via Bagni Vecchi, 1, 82037 Telese Terme (BN), Italy
e-mail: anna.estraneo@icsmaugeri.it

L. Trojano
Neuropsychology Laboratory, Department of Psychology,
University of Campania 'Luigi Vanvitelli',
Viale Ellittico 31, 81100 Caserta, Italy

C. Schnakers, S. Laureys (eds.), *Coma and Disorders of Consciousness*,
DOI 10.1007/978-3-319-55964-3_2

Introduction

After severe acquired brain injuries, survivors may remain in a clinical condition of wakefulness without awareness, known as vegetative state (VS) (or, recently called unresponsive wakefulness syndrome—UWS) [1], in which eyes are open but there is no evidence of consciousness as manifested by volitional responses [2]. Within the continuum from VS to full awareness, patients may remain in an intermediate state, called minimally conscious state (MCS) [3], in which they show minimal, inconsistent but clearly discernible signs of responsiveness. On the basis of the complexity of patients' behaviors, Bruno and colleagues [4] recently proposed a subcategorization of MCS patients into "MCS minus" (MCS−; patients with low-level intentional behavior, such as visual pursuit or localization of noxious stimulation) and "MCS plus" (MCS+; patients with high-level behavioral interactions, such as command following).

Although both clinical conditions (VS/UWS and MCS) are often transitional states between coma and higher levels of consciousness, some patients fail to fully recover self and environmental awareness and show prolonged disorders of consciousness (DOC) that might last a lifetime. Prevalence rates of prolonged DOC are difficult to estimate because of the lack of systematic studies [5]. Notwithstanding the lack of conclusive epidemiological data, it is commonly thought that incidence and prevalence of patients with prolonged DOC is progressively increasing, paradoxically, thanks to improvements of medical intervention techniques in the acute stage. As a consequence, long-term management of these patients has growing clinical, economic, and ethical impact [6, 7]. In this context, to comprehend the evolution of these severe clinical conditions and to identify reliable prognostic markers would allow clinicians and patients' family to make appropriate decisions concerning treatment and care.

Evolution

Since the definition of VS [8], several studies addressed clinical evolution of DOC. However, to date, the clinical outcome of DOC patients is not yet well defined, because most patients quickly leave the medical system to be transferred at home or admitted into chronic facilities and to be taken care by their own families or by nonspecialized caregivers. Moreover, available outcome studies are not conclusive because settings (e.g., neurointensive care units vs. rehabilitation units), study samples (patients with different etiologies and time from injury), length of follow-up, and outcome measures often differ greatly. In a comprehensive review, Bruno [9] included 18 studies on mortality and recovery rates of traumatic and non-traumatic DOC, but most of these studies were quite dated and focused on VS/UWS only, since they have been performed before the diagnostic criteria for MCS have been established [3]. Even the pivotal epidemiological study on prognosis completed by

the Multi-Society Task Force for VS [2] reported on DOC patients without distinguishing the two clinical conditions. According to this study, probability of recovering full consciousness differed as a function of patients' age at onset and etiology and was very low, if not virtually absent, beyond 12 months after traumatic brain injury (TBI) and 6 months after non-traumatic injury. On the basis of these considerations, the term of "permanent" VS has been proposed [2], to classify VS/UWS patients in apparently irreversible unconscious clinical state. Indeed, at that time, only occasional case reports were available about late recovery of consciousness beyond the above temporal limits and prevalently in post-traumatic patients [10]. However, likely thanks to continuous improvements of preventive [11] and restorative therapeutic strategies [12–15], ideas on clinical evolution in DOC patients progressively changed. In 1995, the American Congress of Rehabilitation Medicine suggested avoiding strong time-based prognostic statements (i.e., not to use the term "permanent") even when time elapsed after onset was longer than the time limits proposed by the MSTF [16]. More recently, further case reports [17–19] and cohort studies [20–22] have documented late recovery of variable levels of consciousness beyond the classical temporal limits even in vascular and anoxic VS/UWS patients. Therefore, late emergence from VS/UWS or recovery of full consciousness cannot be longer considered as an exception even well beyond time limits proposed by the MSTF, independently of etiology although probability of late recovery is thought to be higher in traumatic VS/UWS patients and strongly associated with younger age [21, 22].

In patients who regained some level of consciousness at a late time, clinical and neuropsychological conditions might further progress in subsequent years, although improvements are often minimal, and most patients are affected by severe functional disability [20–23]. In a cohort of patients who recovered responsiveness and eventually full consciousness beyond 1 year post-onset, a 5-year follow-up [23] showed that all recovered patients were very severely disabled and bore a considerable weight of secondary pathologies due to long-lasting immobility. All of them required support and care 24 h a day and were fully dependent in common daily life activities.

These findings would suggest that some kind of brain plasticity could not be excluded even for a long time after a severe brain injury. However, the occurrence of severe motor and cognitive deficits in "late-recovered" patients suggests that there is a need for early appropriate level of rehabilitation, since from the acute phase in intensive care unit. This could facilitate recovery of responsiveness and minimize motor disabilities (e.g., contractures, joint limitations) [24] that negatively influence functional independence and quality of life of patients and of their families [25].

The proposal of clinical criteria for identifying MCS [3], and subsequent advancements in diagnostic accuracy for distinguishing MCS from VS/UWS patients [26–28] shed new light on clinical evolution of DOC patients. Indeed, several recent studies [9, 22, 24, 29–32] distinguished VS/UWS from MCS patients and found that prognosis differed as a function of clinical diagnosis (Table 2.1). In general, it has been observed that MCS patients have a higher probability of clinical

Table 2.1 Evolution of minimally conscious state patients in studies on outcomes of prolonged disorders of consciousness (published after 2002)

First author	Patients (number)	Etiology	Time post-onset (months)	Follow-up (years)	Results	Note
Eilander [29][a]	VS/UWS or MCS (145)[b]	TBI, nTBI	<6	0.3	Almost two-thirds of the patients reached full consciousness	More favorable outcome in TBI and in MCS
Lammi [30]	MCS (18)	TBI	1.5	2–5	10% dead, 20% extremely severe to VS/UWS (2 of them remained in MCS), 55% severe to moderate disability, 15% partial or mild disability (outcome measure: DRS)	High proportion of patients was functionally independent in BDA
Katz [31][a]	VS/UWS (11), MCS (25)	TBI, nTBI	1	1–4	80% emerged from MCS after 7.6 weeks without significant difference between TBI and nTBI, and 70% of them cleared CS/PTA by 1 year post-injury	MCS progress 1 year after injury without difference between etiologies
Luaté [32][a]	VS/UWS (12), MCS (39)	TBI, nTBI	12	5	14 died, 9 remained in MCS, and 13 emerged from MCS with severe disabilities (3 were lost to follow-up)	A third of MCS improved more than 1 year after onset, but remained severely or totally disabled

Table 2.1 (continued)

First author	Patients (number)	Etiology	Time post-onset (months)	Follow-up (years)	Results	Note
Bruno [9][a]	VS/UWS (116), MCS (84)	TBI, nTBI	1	1	TBI: 23% dead, 48% eMCS; non-TBI: 33% dead, 26% eMCS	Better (but not significantly) outcome in TBI
Seel [24][a]	Coma (2), VS/UWS (41), MCS (57)	TBI, nTBI	1–3	0.1–0.8	12% remained in VS, 35% remained in MCS, 53% emerged from MCS	eMCS was more frequent in patients with TBI and high CRS-R score
Steppacher [22][a]	VS/UWS (59) MCS (43)	TBI, anoxic, other	1–3	8±3.5	35% dead, 23 % remained in MCS, 42% recovered ability to functionally communicate within 3 months (only 4.6% recovered later)	Most of MCS recovered within the first few months

Note: *VS/UWS* vegetative state/unresponsive wakefulness syndrome, *MCS* minimally conscious state, *TBI* traumatic brain injury, *nTBI* non-traumatic brain injury, *DRS* disability rating scale, *CS/PTA* confusional state/post-traumatic amnesia, *CRS-R* coma recovery scale-revised [26], *BDA* basic daily activities, *eMCS* emergence from minimally conscious state

[a]Denotes the studies demonstrating that clinical outcome was significantly better in minimally conscious state than in vegetative state patients

[b]This study included only individuals age <25 years

improvement, a better outcome in terms of functional independence in basic daily activities [9, 22, 24, 29, 31, 32], and a longer life expectancy than VS/UWS patients [9, 22, 32], consistent with the idea that MCS is characterized by relatively spared structural and functional brain connectivity with respect to VS/UWS [33].

To contribute and to comprehend the clinical evolution of DOC, we followed a large sample of prolonged VS/UWS and MCS patients admitted to intensive rehabilitation unit and gathered data about the clinical outcome at 12 and at 24 months post-injury. Our main aim was to ascertain whether evolution in DOC varies in relationship to the three most frequent etiologies (i.e., traumatic, vascular, or anoxic brain injury). In this respect, it is classically maintained that evolution in

post-traumatic DOC patients is more favorable than that observed in non-traumatic etiology, both in short- [2, 9, 24, 29, 32] and in long-term [21, 22] survival and recovery of consciousness, but mixed data have been reported about the possible relationships between etiology and clinical recovery in MCS patients (see Table 2.1). Moreover, most of the available studies contrasted patients with traumatic etiology with those of non-traumatic origin, without distinguishing between anoxic and vascular etiology.

Our sample included patients admitted to our neurorehabilitation unit in VS/UWS ($n = 131$) or in MCS ($n = 64$). Inclusion criteria for the study were diagnosis of VS/UWS or MCS on repeated clinical evaluation according to standard diagnostic criteria [2, 3]; severe traumatic, anoxic, or vascular brain injury; time from onset ≥3 months; and age ≥18 and ≤80 years. We excluded patients with mixed etiology (e.g., both traumatic and anoxic brain injury) and with premorbid history of psychiatric or neurodegenerative diseases. In all patients, the diagnosis was supported by repeated administration of the Italian Version of Coma Recovery Scale-Revised [26, 34]. The clinical assessment at 12 and 24 months post-onset was performed by direct observation, and outcome corresponded to clinical diagnosis of VS/UWS, MCS, and emergence from MCS (eMCS) according to standard criteria [2, 3], or to death.

Clinical evolution in this sample (Table 2.2) would substantially confirm that clinical outcome is better in MCS than in VS/UWS group (chi = 60.82, df = 3, $p < 0.001$) and in traumatic VS/UWS than in anoxic or in vascular VS/UWS patients (chi = 12.85, df = 6, $p = 0.048$), in line with previous recent studies on DOC patients [2, 9, 21, 22, 24, 29, 32]. It should be noted that no MCS patient returned to VS/UWS during the follow-up period, in contrast with Bruno et al. [9]. Moreover, in MCS patients, the etiology was not associated to differences in clinical outcome at 1 or 2 years post-onset (chi = 4.46, df = 4, $p = 0.348$). This finding is consistent with data reported in two previous studies [9, 22] and might suggest that the severity of anoxic brain damage, and the detrimental conditions usually associated with vascular etiology (e.g., older age and premorbid coexisting diseases such as diabetes, hypertension, or dyslipidemia) could hamper survival and awakening in VS/UWS patients, whereas etiological factors play a relatively little role in MCS patients.

The analysis of clinical evolution in our patients also suggested that VS/UWS patients tend to show a relatively slower recovery than MCS patients. Indeed, VS/UWS patients showed some progression in their clinical conditions between 1 and 2 years post-onset, although most of these patients recovered responsiveness (i.e., they evolved to MCS) and only a few emerged from MCS. The majority of MCS patients who recovered full consciousness did so within the first year after onset, whereas between 1 and 2 years post-onset only very few MCS patients showed an improvement in terms of changes in clinical diagnosis (i.e., emergence from MCS). These observations would fit with data reported by Steppacher [22] and substantially by Luauté [32] and suggest that the potential of recovery in MCS patients is higher in the first year post-onset, when some of them regain high-level cognitive abilities such as functional communication. Further improvements in MCS patients might be captured by

Table 2.2 Clinical evolution in patients in vegetative state/unresponsive wakefulness syndrome ($n = 131$) or in minimally conscious state ($n = 64$) with various etiologies

Months	4	6	12	18	24
VS/UWS—traumatic ($n = 34$)					
Dead	0	3	8	9	13
VS/UWS	28	23	18	14	12
MCS	6	8	4	6	2
eMCS	0	0	4	5	7
VS—anoxic ($n = 67$)					
Dead	2	11	22	27	30
VS/UWS	64	49	35	27	24
MCS	1	7	10	12	10
eMCS	0	0	0	1	3
VS—vascular ($n = 64$)					
Dead	7	16	27	35	36
VS/UWS	49	38	25	20	19
MCS	8	8	9	6	6
eMCS	0	2	3	3	3
MCS—traumatic ($n = 23$)					
Dead	1	2	3	4	4
MCS	21	16	11	9	9
eMCS	1	5	9	10	10
MCS—anoxic ($n = 14$)					
Dead	1	4	5	6	7
MCS	12	8	6	4	3
eMCS	1	2	3	4	4
MCS—vascular ($n = 27$)					
Dead	1	3	5	6	9
MCS	24	16	9	8	8
eMCS	3	8	13	13	10

VS/UWS vegetative state/unresponsive wakefulness syndrome, *MCS* minimally conscious state, *eMCS* emergence from minimally conscious state

finer-grained assessment tools sensitive to levels of responsiveness, such as those distinguishing MCS− from MCS+ patients [4], whereas clinical diagnosis alone might overlook more subtle, and important clinical changes. Indeed, it has been repeatedly reported that MCS patients can show clinical improvements later than 1 year post-injury [22, 31, 32], and even many years post-onset [35], though with severe motor and cognitive sequelae [32]. The present observations thus underline that prognostic statements in MCS should be made with caution [30, 36] and encourage development of tailored treatment for MCS patients (including brain stimulation techniques; [12, 37]) to promote recovery of full consciousness and minimize motor disabilities. It is advisable to perform long-term monitoring of DOC patients and in particular of MCS patients in order to fully comprehend clinical evolution of these severe clinical conditions and to

pursue optimal rehabilitation treatments, in terms of intensity and duration. For this purpose, cooperative systematic studies in large groups of prolonged DOC patients with a long-term follow-up seem strongly needed.

Prognostic Issues

To identify valid prognostic markers for clinical management of DOC patients appears to be very challenging. As briefly mentioned above, to date knowledge about clinical evolution as a function of patients' etiology, age, and clinical diagnosis of VS/UWS or MCS is not sufficiently robust to provide reliable information to guide clinicians and patients' family in decision-making processes. In this context, many clinical markers have been tested as potential predictors of overall clinical outcome (i.e., mortality and recovery of consciousness) to be routinely used in clinical management of DOC patients. Many studies on prognosis of DOC patients focused on early clinical and instrumental indicators recorded in comatose patients and aimed to predict outcome within 6–12 months after brain injury. Large group studies have identified some clinical and para-clinical variables associated to outcome with relatively high sensitivity and specificity, but it remains very difficult to predict outcome at the single case level. For instance, in 2006, the American Academy of Neurology published an algorithm in anoxic brain injured patients for cardiac arrest based on some variables recorded within the first week that would predict poor outcome (i.e., death or progression to VS/UWS after 1 month) with considerable efficiency: (1) the absence of pupillary reactions to light or corneal reflexes, (2) extensor or no motor response to pain after 3 days of observation, (3) myoclonus status epilepticus, (4) serum neuron-specific enolase higher than 33 g/L, and (5) bilateral absence of N20 cortical component of somatosensory evoked potential (SEPs) [38]. Among these predictors, bilateral absence of SEP cortical component recorded on day 1 following anoxic injury is considered the most accurate marker for poor prognosis above all in comatose patients [39], whereas the presence of spared SEP bilaterally has a strong positive prognostic value for recovery only in post-traumatic patients [40, 41]. Prognostic value of neurophysiological assessment increases if long-latency auditory event-related potentials (ERPs) are also taken into account. In a meta-analysis, the presence of positive component occurring 300 ms after the stimulus (P300, modulated by arousal and attention) and the mismatch negativity (MMN, generated by an automatic mechanism in response to a deviant tone in an otherwise repetitive auditory stimulus) appeared to be reliable predictors of recovery of consciousness in comatose patients following vascular, traumatic, and metabolic encephalopathy [42]; the presence of MMN seems also to predict recovery of consciousness in anoxic comatose patients after cardiac arrest [43]. An additional long-term prognostic study showed that clinical and neurophysiological variables recorded at the early stage of coma (i.e. age over 39 years and absence of cortical components of middle-latency auditory evoked potentials) were associated with high likelihood of poor outcome in traumatic and

non-traumatic DOC patients [32] and suggested that the strong relationship between auditory evoked potentials and recovery of consciousness might be indicative for the (initial) consolidation of neural networks underlying (communicative) ability of patients' interaction with environment [44].

Despite this strong evidence about prognostic value of clinical and neurophysiological markers in comatose brain injured patients, instrumental markers such as SEP are rarely recorded in the intensive care units, and it is also a common experience that data about acute phase are not entirely forwarded to the physicians involved in the next steps of the care pathway. As a result for the neurorehabilitation team, it is very difficult to provide solid indication about the possible outcome of patients who remain in VS/UWS or MCS more than 1 month post-onset and to suggest the most appropriate level of care. For this purpose, the neurorehabilitation team can only rely on data collected at patients' admission at their unit, i.e., generally at 1–3 months post-onset, but prognostic studies on markers recorded in this time window did not provide conclusive information about clinical outcome in VS/UWS or MCS patients (Table 2.3), because of several methodological limitations: low number of patients, outcome measures insufficient to detect initial recovery of consciousness (i.e., to diagnose MCS), retrospective analysis of data collected elsewhere, and analysis of variables not easy to be routinely collected in the neurorehabilitation setting (e.g., functional neuroimaging, quantitative analysis of EEG). Moreover, the majority of available studies evaluated the impact of prognostic factors on recovery of responsiveness/consciousness within 12 months after brain injury (Table 2.3). However, outcome at 12 months post-onset cannot be considered as definitive, since further progression of clinical conditions is considered possible, particularly in patients with traumatic brain injury. Finally, many of the available short-term outcome studies provided predictors of rapid recovery of consciousness gathered in case series including patients with moderate brain injury; conclusions drawn in these studies might not apply to patients with more severe brain injuries who remain in VS/UWS or MCS for a longer period.

The overall pattern of prognostic studies performed in the rehabilitative phase (Table 2.3) was partially consistent with conclusions drawn in studies addressing the acute phase (prognostic value of SEPs), but also revealed several peculiarities underlining that specific markers recorded in the rehabilitative phase seem useful to predict long-term outcome. For instance, a recent prospective 2-year study demonstrated that the presence of N20 and high level of responsiveness (Coma Recovery Scale-Revised total score of 6 or higher) recorded more than 1 month after anoxic brain injury were predictors of recovery of responsiveness at 24 months post-onset in a cohort of anoxic VS/UWS patients [50]. Additional long-term prognostic studies showed that high amplitude and short latency of MMN elicited by sound [65] and presence of late component (N400) elicited by speech [67] recorded in VS/UWS could predict recovery of consciousness and functional outcome 2 years after injury. These noteworthy results reported by long-term studies confirm that multimodal neurophysiological assessment (by means of auditory cognitive and somatosensory evoked potentials) can establish integrity or impairment of cortical neural pathways, thus providing useful information for long-term prognostic evaluation

Table 2.3 Summary of most recent studies (2005–2016) on prognostic factors in prolonged disorders of consciousness

First author	Patients (number)	Time post-onset (months)	Follow-up length (years)	Marker	Outcome
TBI					
Whyte [45]	VS/UWS or MCS (124)	1–4	0.3 post-onset	High DRS score at enrollment, high DRS score change over the first 2 weeks	Recovery of command following
Xu W [46]	VS/UWS (58)	>1	1 post-onset	Presence of SEPs	Progress to MCS and death
Cavinato [47]	VS/UWS (34)	2–3	1	Presence of P300	Recovery of consciousness
Qin [48]	VS/UWS (56), MCS (29)	3–5	0.3	DMN (PCC-LLPC) connectivity on fMRI	Recovery of consciousness
Anoxic					
Boccagni [49]	VS/UWS (12), MCS (1), eMCS (2)	<0.1–3	0.3	Standard EEG Synek score 1 and 2	LCF score improvement
Estraneo [50]	VS/UWS (43)	1–6	2 post-onset	CRS-R total score ≥6, presence of SEPs	Recovery of consciousness
Hildebrandt [51]	VS/UWS (21)	<0.1–4	NA	Presence of N100 and VEP, higher perfusion in the visual cortex and in the precuneus on SPECT	Emergence from VS/UWS
All etiologies					
Eilander [29]	VS/UWS or MCS (145)	<6	0.8	Clinical diagnosis, traumatic etiology, and interval from injury	Recovery of consciousness
Dolce [52]	VS/UWS (303)	NA	0.5	Reappearance of spontaneous motility, eye tracking and oculo-cephalic reflex and disappearance of oral automatisms	Improvement of GOS
Whyte [53]	VS/UWS or MCS (169)	1–4	0.3 post-onset	Time post-injury, DRS score at study entry	Recovery of command following
Weiss N [54]	VS/UWS (26)	<0.1	0.1–0.7	Presence of fast component of nystagmus during caloric vestibulo-ocular response	Recovery of consciousness

Table 2.3 (continued)

First author	Patients (number)	Time post-onset (months)	Follow-up length (years)	Marker	Outcome
Steppacher [22]	VS/UWS or MCS (43)	2–3	5–10 post-onset	Young age, care at home, traumatic etiology	Emergence from VS/UWS
Babiloni [55]	VS/UWS (50)	1–3	0.3	Cortical sources of resting alpha rhythms at EEG	Recovery of consciousness
Bagnato [56]	VS/UWS (25), MCS (16),	1–3	0.3	EEG Synek scores 1 and 2	Improvement of LCF score
Logi [57]	VS/UWS or MCS (50)	<2	0.5	Presence of EEG reactivity to painful stimuli	Recovery of consciousness
Sarà [58]	VS/UWS (38)	1–2	0.6	EEG approximate spectral entropy	Recovery of consciousness
Fingelkurts [59]	VS/UWS (14)	3	0.5	Number and strength of cortical functional connections between EEG segments	Recovery of consciousness
Rosanova [60]	VS/WS (5)	0.5–2	0.5	Effective neuronal connectivity (on TMS/EEG)	Recovery of consciousness
Kang XG [61]	VS/UWS (56)	1–3	1	Presence of motor response, EEG reactivity, sleep spindles and SEPs	Clinical recovery
Bagnato [62]	VS/UWS (59); MCS (47)	1–2	0.3	High EEG amplitude, alpha frequency and EEG reactivity (low EEG amplitude, delta frequency, and no EEG reactivity predict poor outcome)	Improvement of CRS-R total score
Schorr [63]	VS (58), MCS (15)	<0.1–177	1	High parietal delta and theta and high frontoparietal theta and alpha coherence on EEG	Recovery of consciousness
Kotchoubey [64]	VS/UWS (50), MCS (38) severely brain-damaged Con (10)	1–127	0.5	Presence of MMN on ERP	Clinical improvement
Wijnen [65]	VS/UWS (10)	1–5	2 post-onset	MMN amplitude >1 μV on ERP	Recovery of consciousness

(continued)

Table 2.3 (continued)

First author	Patients (number)	Time post-onset (months)	Follow-up length (years)	Marker	Outcome
Qin [66]	Coma (4), VS/UWS (6), MCS (2)	>1	0.3	Presence of SON-MMN on ERP	Recovery of consciousness
Luautè [32]	VS/UWS (12), MCS (28)	12	5	N100 on ERP (absence of MLAEPs predicts poor outcome). Of note MLAEP and N100 were recorded in comatose phase	Recovery of consciousness in MCS
Steppacher [67]	VS/UWS (53), MCS (39)	<12	2–17	Presence of N400 elicited by semantic deviance in spoken language on ERP	Recovery of consciousness
Rohaut [68]	VS/UWS (15), MCS (14)	<1–52	12	Presence of N400 and LPC on ERP	Recovery of consciousness
Li [69]	Coma (2), VS/UWS (6), MCS (5)	1.6–21	1	P300 in TO and DO paradigms (lack of P300 in TO paradigm predicts poor prognosis)	Recovery of consciousness
Di [70][b]	VS/UWS (48)	<0.1–13	0.3–0.6	Atypical activation patterns during active paradigm on fMRI or PET	Recovery of consciousness
Coleman [71]	VS/UWS (22), MCS (19)	0.1–4	0.5	Auditory activation on fMRI	Recovery of consciousness
Vogel [72]	VS/UWS (10), MCS (12)	1–6	0.1–1	Activation during mental imagery on fMRI	Recovery of consciousness
Stender [73]	VS/UWS (41), LIS (4), MCS (81)	<1–0.9	1	Increased cortical metabolism on (18) F-FDG PET (and activation during mental imagery on fMRI)	Recovery of consciousness
Li L [74]	VS/UWS (10), MCS (12)	1–2	1	Presence of fMRI activation in midbrain, thalamus, or primary and/or second somatosensory cortex and EEG reactivity to thermal stimulation	Improvement of mGOS score

Table 2.3 (continued)

First author	Patients (number)	Time post-onset (months)	Follow-up length (years)	Marker	Outcome
Wang [75]	VS/UWS (39), MCS (25), eMCS (2)	1–60	1	Activation in auditory cortex elicited by SON on fMRI	Recovery of consciousness in traumatic VS/UWS
Wu [76]	Coma (14), VS/UWS (18), MCS (27), Con (40)	<1–22	0.3	Resting-state FCS in DMN on fMRI	Recovery of consciousness

Note: *TBI* traumatic brain injury, *VS/UWS* vegetative state/unresponsive wakefulness syndrome, *MCS* minimally conscious state, *DRS* disability rating scale [77], *SEPs* somatosensory evoked potentials, *DMN* default mode network, *PCC-LLPC* posterior cingulate cortex-left lateral parietal cortex, *fMRI* functional magnetic resonance imaging, *eMCS* emergence from minimally conscious state, *EEG* electroencephalogram, *LCF* level of cognitive functioning [77], *CRS-R* coma recovery scale-revised [26], *NA* not available, *VEP* visual evoked potentials, *SPECT* single photon emission computed tomography, *GOS* Glasgow Outcome Scale [78], *TMS* transcranial magnetic stimulation, *Con* conscious, *MMN* mismatch negativity; *SON* subject's own name, *ERP* event-related potentials, *MLAEPs* middle-latency auditory evoked potentials, *LPC* late positive component on ERPs also described as P600, *TO* tone (1 Hz tone as standard stimuli) and subject's own name (as deviant stimuli), *DO* subject's derived name (as a standard stimulus) and subject's own name (as a deviant stimulus), *PET* positron emission tomography, *LIS* locked-in syndrome, *FCS* functional connectivity strength, *mGOS* modified Glasgow Outcome Scale [74]
This article reviewed 15 neuroimaging studies (1997–2007) that analyzed cortical activation in fMRI (17 patients) or PET imaging (32 patients) during active paradigms (e.g., mental imagery, hearing speech) in vegetative state patients. Cortical activation was classified as "typical" activation of "low-level" primary sensory cortices and "atypical" activation spreading to "higher-level" associative cortices

and rehabilitation planning of DOC patients. In particular, auditory event-related potential components are generated in brain areas (e.g., superior and middle temporal gyri) that showed significant functional connectivity with other brain areas on functional magnetic resonance imaging (fMRI) after auditory stimulation in MCS patients [79].

In neurorehabilitation units standard EEG represents a low-cost neurophysiological method widely used and easy to repeat and analyze. Standard EEG is relevant to monitor clinical evolution in DOC patients, for instance, by quantifying the amount of alpha rhythm as a sign of integrity of thalamocortical connections, which are related to wakefulness and consciousness [14]. Visual analysis of standard EEG has been extensively applied in comatose anoxic patients and its prognostic usefulness well established in these patients [38, 80–82], whereas only few EEG studies were performed in prolonged DOC patients. Two EEG studies [49, 56] showed a significant correlation between specific EEG patterns classified by Synek's score [82] and awakening in VS/UWS at about 3 months after traumatic or non-traumatic brain injury. On the contrary, using a longer follow-up period (i.e., 24 months post-onset) and a more accurate diagnostic scale able to identify early clinical signs of recovery (i.e., CRS-R), a study reported recovery of responsiveness also in some

VS/UWS patients with a EEG pattern classified as "malign" by the Synek scale [21]. The lack of specificity of the Synek scale (which was developed for patients in coma rather than for patients with VS/UWS or in a MCS) should be taken into account. Furthermore, the Synek scale includes some EEG patterns (e.g., theta coma and alpha coma) that are not found in patients with prolonged DOC. On this basis, recent studies analyzed classical EEG parameters without referring to Synek scale (i.e., EEG reactivity, amplitude and frequency of background activity) and demonstrated the prognostic value of such parameters, particularly when combined together, for predicting short-term outcome in VS/UWS and MCS patients following traumatic, vascular, or anoxic injury [57, 62]. Further studies, possibly using EEG classification criteria more refined and specifically addressing long-term outcome, are necessary to clarify the prognostic value of standard EEG, also taking into account its large susceptibility to metabolic changes and drugs.

It should be underlined that sophisticated analysis of EEG activity (e.g., quantitative analysis of EEG power spectra) could provide strong prognostic markers of recovery in DOC patients, although they are not commonly available in neurorehabilitative settings. For instance, reduction of EEG complexity and mutual interconnectivity (i.e., reduced EEG approximate spectral entropy) [58] may serve as a predictor for poor clinical outcome in VS/UWS patients, whereas the power of alpha rhythm on occipital source, estimated on resting EEG by low-resolution electromagnetic tomography [55] or high neuronal connectivity between different brain areas evaluated by EEG coherence analysis (e.g., high parietal delta and theta and high frontoparietal theta and alpha coherence) [63] or complexity in connectivity measured by means of transcranial magnetic stimulation combined with high-density EEG [60], provided strong early evidence for recovery from VS/UWS.

Last, modern advanced neuroradiological techniques offer novel insight into the pathophysiology and recovery of DOC patients, providing potentially relevant prognostic information [70, 83], although the use of these techniques is at the moment limited to highly specialized settings. In particular, detection of "atypical" activation spreading to "higher-level" associative cortices by means of PET or fMRI study during passive stimulation paradigms or active cognitive tasks has been associated to eventual recovery of consciousness [70]. However, it has been claimed that even fMRI techniques might be unable to detect regional cortical activation in patients with VS/UWS, due to technical limitations (e.g., patent moving during the scan) or specific patients' cognitive deficits which can impair the ability to carry out tasks employed in experimental paradigms (e.g., receptive language impairments). These potential limitations of the use of fMRI based on active experimental paradigms could be overcome by adopting modern neuroimaging techniques that analyze structural connectivity (diffusion tensor imaging, DTI), and above all functional connectivity in the resting brain ("resting-state" fMRI and cerebral (18) F-fluorodeoxyglucose PET). Indeed, metabolic cerebral integrity on (18)F-FDG PET imaging predicts better clinical outcome than fMRI during mental activation tasks [73]. Using these techniques, it is possible to investigate the functioning of the

neural network that recent studies suggest to be related to the awareness state, the so-called default-mode network (DMN) or intrinsic network [84]. This neural network includes precuneus, medial frontal cortex, and the temporo-parietal junction bilaterally and is consistently characterized by a high activation at rest (and a deactivation during most cognitive tasks); it has been considered mainly involved in self-representation, episodic memory, mind wandering, and stimulus-independent thoughts. The study of spontaneous neural activity in "resting state" in DOC patients might contribute to better understand the neural mechanisms responsible for awareness and also provide prognostic information, since preservation of functional connectivity in the DMN was related to the recovery of consciousness in VS/UWS patients after 3 months [48].

At the end of this paragraph on prognostic issues, it is important to stress that both simple and sophisticated tools are useful to delineate potential for recovery and can help in estimating likelihood of clinical improvement. However, the evolution of chronic and highly complex clinical conditions such as DOC can be heavily affected by various factors (e.g., clinical complications, negative effects of pharmacological therapy) that could unpredictably influence patients' clinical evolution, regardless of any known predictive marker. Several clinical complications in DOC seem to be directly related to brain damage, such as paroxysmal sympathetic hyperactivity, spasticity, or epileptic seizures, whereas others are linked to concurrent severe cognitive and motor disability, such as respiratory infections or pressure sores. Such clinical complications occur frequently in DOC patients a few months after brain injury, since it has been documented in a large multicentric study with patients of traumatic etiology [85]. Occurrence of severe comorbidities, such as pneumonia, paroxysmal sympathetic hyperactivity, or arrhythmias without organic heart diseases, might interfere with survival and cognitive and functional outcome at 1 year of follow-up in DOC patients [86, 87]. The most common medical complications are active seizures during inpatient acute care hospitalization or inpatient rehabilitation (46% of DOC patients). Seizures were associated with lower scores of functioning (FIM) at 1 year [86]. A prospective study on 130 traumatic, vascular, and anoxic DOC patients and with a clinical diagnosis of VS/UWS ($n = 97$) or MCS ($n = 33$), confirmed that unprovoked remote epileptic seizures occur in about one-third of the patients during neurorehabilitation stay. Moreover, occurrence of epileptic seizures did not significantly influence mortality rates but was significantly related to recovery of consciousness and level of responsiveness for long-term outcome (30 months post-onset) [88].

Such preliminary data concur with the few available studies on comorbidities in prolonged DOC patients stressing that clinical complications can play an important role in determining the long-term clinical outcome. Further studies seem necessary to assess the occurrence of intervening factors and to optimize tailored therapeutic interventions to manage them. Indeed, clinical complications require appropriate clinical expertise for optimal management, since their effective treatment might reduce further clinical and neurological complications and mortality [24].

Conclusion

When determining prognosis in DOC patients, clinicians have to consider several patients' factors: the pathological mechanism causing clinical condition of VS/UWS or MCS (i.e., etiology), the age of the patient (likely influencing the physiological process of recovery, e.g., brain plasticity), the duration of disorder of consciousness (likely related to the severity of brain damage), the findings of structural and functional integrity of neuronal populations (as assessed by neurophysiological and neuroimaging methods), and the presence of clinical complications that could impact care strategies.

Previous studies have searched for robust prognostic markers based on clinical and ancillary testing in VS/UWS patients, but reliable markers to characterize DOC patients who will present late recovery have not been identified. Long-term evolution of MCS patients has not been established, and definite prognostic information is not available for these patients. Yet determining an evidence-based prognosis would allow an optimization of the level of care for patients with high potential for recovery.

For these reasons, prospective longitudinal systematic investigations of outcome in large groups of individuals with prolonged DOC (VS/UWS and MCS) and with various etiologies are needed to better clarify the natural history of DOC. In such studies, the combination of clinical, anamnestic, and instrumental data recorded over a long time post-onset can contribute to define prognostic markers and update current positions on medical, ethical, and legal issues connected with management and care of DOC patients.

References

1. Laureys S, Celesia GG, Cohadon F, Lavrijsen J, León-Carrión J, Sannita WG, et al.; European Task Force on Disorders of Consciousness. Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. BMC Med. 2010;8:68. doi: 10.1186/1741-7015-8-68.
2. Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state (1). N Engl J Med. 1994;330:1499–508.
3. Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, et al. The minimally conscious state: definition and diagnostic criteria. Neurology. 2002;58:349–53.
4. Bruno MA, Vanhaudenhuyse A, Thibaut A, Moonen G, Laureys S. From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness. J Neurol. 2011;258:1373–84.
5. Pisa FE, Biasutti E, Drigo D, Barbone F. The prevalence of vegetative and minimally conscious states: a systematic review and methodological appraisal. J Head Trauma Rehabil. 2014;29(4):E23–30. doi:10.1097/HTR.0b013e3182a4469f.
6. Bernat JL. Chronic disorders of consciousness. Lancet. 2006;367:1181–92.
7. Whyte J. Treatments to enhance recovery from the vegetative and minimally conscious states: ethical issues surrounding efficacy studies. Am J Phys Med Rehabil. 2007;86:86–92.

8. Jennett B, Plum F. Persistent vegetative state after brain damage. A syndrome in search of a name. Lancet. 1972;1:734–7.
9. Bruno MA, Ledoux D, Vanhaudenhuyse A, Gosseries O, Thibaut A, Laureys S. Prognosis of patients with altered state of consciousness. In: Schnakers C, Laureys S, editors. Coma and disorders of consciousness. London: Springer; 2012. p. 11–23.
10. Childs NL, Mercer WN. Late improvement in consciousness after post-traumatic vegetative state. N Engl J Med. 1996;334:24–5.
11. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med. 2002;346:549–56.
12. Thibaut A, Di Perri C, Chatelle C, Bruno MA, Bahri MA, Wannez S, et al. Clinical response to tdcs depends on residual brain metabolism and grey matter integrity in patients with minimally conscious state. Brain Stimul. 2015;8:1116–23. doi:10.1016/j.brs.2015.07.024.
13. Giacino JT, Khademi A, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. N Engl J Med. 2012;366:819–26. doi:10.1056/NEJMoa1102609.
14. Estraneo A, Pascarella A, Moretta P, Loreto V, Trojano L. Clinical and electroencephalographic on-off effect of amantadine in chronic non-traumatic minimally conscious state. J Neurol. 2015;262:1584–6. doi:10.1007/s00415-015-7771-y.
15. Lanzillo B, Loreto V, Calabrese C, Estraneo A, Moretta P, Trojano L. Does pain relief influence recovery of consciousness? A case report of a patient treated with ziconotide. Eur J Phys Rehabil Med. 2016;52:263–6.
16. American Congress of Rehabilitation Medicine. Recommendations for use of uniform nomenclature pertinent to patients with severe alterations in consciousness. Arch Phys Med Rehabil. 1995;76:205–9.
17. Faran S, Vatine JJ, Lazary A, Ohry A, Birbaumer N, Kotchoubey B. Late recovery from permanent vegetative state heralded by event-related potentials. J Neurol Neurosurg Psychiatry. 2006;77:998–1000.
18. Sancisi E, Battistini A, Di Stefano C, Simoncini L, Simoncini L, Montagna P, et al. Late recovery from post-traumatic vegetative state. Brain Inj. 2009;23:163–6. doi:10.1080/02699050802660446.
19. Avesani R, Gambini MG, Albertini G. The vegetative state: a report of two cases with a long-term follow-up. Brain Inj. 2006;20:333–8.
20. Nakase-Richardson R, Whyte J, Giacino JT, et al. Longitudinal outcome of patients with disordered consciousness in the NIDRR TBI Model Systems Programs. J Neurotrauma. 2012;29:59–65.
21. Estraneo A, Moretta P, Loreto V, et al. Late recovery after traumatic, anoxic, or hemorrhagic long-lasting vegetative state. Neurology. 2010;75:239–45.
22. Steppacher I, Kaps M, Kissler J. Will time heal? A long-term follow-up of severe disorders of consciousness. Ann Clin Transl Neurol. 2014;1:401–8. doi:10.1002/acn3.63.
23. Estraneo A, Moretta P, Loreto V, Santoro L, Trojano L. Clinical and neuropsychological long-term outcomes after late recovery of responsiveness: a case series. Arch Phys Med Rehabil. 2014;95:711–6. doi:10.1016/j.apmr.2013.11.004.
24. Seel RT, Douglas J, Dennison AC, Heaner S, Farris K, Rogers C. Specialized early treatment for persons with disorders of consciousness: program components and outcomes. Arch Phys Med Rehabil. 2013;94:1908–23. doi:10.1016/j.apmr.2012.11.052.
25. Moretta P, Estraneo A, De Lucia L, Cardinale V, Loreto V, Trojano L. A study of the psychological distress in family caregivers of patients with prolonged disorders of consciousness during in-hospital rehabilitation. Clin Rehabil. 2014;28:717–25.
26. Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil. 2004;85:2020–9.
27. Schnakers C, Vanhaudenhuyse A, Giacino J, Ventura M, Boly M, Majerus S, Moonen G, et al. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. BMC Neurol. 2009;9:35.
28. Trojano L, Moretta P, Loreto V, Santoro L, Estraneo A. Affective saliency modifies visual tracking behavior in disorders of consciousness: a quantitative analysis. J Neurol. 2013;260:306–8. doi:10.1007/s00415-012-6717-x.

29. Eilander HJ, Wijnen VJ, Scheirs JG, de Kort PL, Prevo AJ. Children and young adults in a prolonged unconscious state due to severe brain injury: outcome after an early intensive neurorehabilitation programme. Brain Inj. 2005;19:425–36.
30. Lammi MH, Smith VH, Tate RL, Taylor CM. The minimally conscious state and recovery potential: a follow-up study 2 to 5 years after traumatic brain injury. Arch Phys Med Rehabil. 2005;86:746–54.
31. Katz DI, Polyak M, Coughlan D, Nichols M, Roche A. Natural history of recovery from brain injury after prolonged disorders of consciousness: outcome of patients admitted to inpatient rehabilitation with 1–4 year follow-up. Prog Brain Res. 2009;177:73–88.
32. Luauté J, Maucort-Boulch D, Tell L, Quelard F, Sarraf T, Iwaz J, et al. Long-term outcomes of chronic minimally conscious and vegetative states. Neurology. 2010;75:246–52. doi:10.1212/WNL.0b013e3181e8e8df.
33. Demertzi A, Antonopoulos G, Heine L, Voss HU, Crone JS, de Los AC, et al. Intrinsic functional connectivity differentiates minimally conscious from unresponsive patients. Brain. 2015;138:2619–31. doi:10.1093/brain/awv169.
34. Estraneo A, Moretta P, De Tanti A, Gatta G, Giacino JT, Trojano L, Italian CRS-R Multicentre Validation Group. An Italian multicentre validation study of the coma recovery scale-revised. Eur J Phys Rehabil Med. 2015;51:627–34.
35. Voss HU, Uluğ AM, Dyke JP, Watts R, Kobylarz EJ, McCandliss BD, et al. Possible axonal regrowth in late recovery from the minimally conscious state. J Clin Invest. 2006;116:2005–11.
36. Hirschberg R, Giacino JT. The vegetative and minimally conscious states: diagnosis, prognosis and treatment. Neurol Clin. 2011;29:773–86. doi:10.1016/j.ncl.2011.07.009.
37. Estraneo A, Pascarella A, Moretta P, Masotta O, Fiorenza S, Chirico G, et al. Repeated transcranial direct current stimulation in prolonged disorders of consciousness: a double-blind cross-over study. J Neurol Sci. 2017;375:464–70. doi:10.1016/j.jns.2017.02.036.
38. Wijdicks EF, Hijdra A, Young GB, et al; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2006;67:203–10.
39. Carter BG, Butt W. Are somatosensory evoked potentials the best predictor of outcome after severe brain injury? A systematic review. Intensive Care Med. 2005;31:765–75.
40. Amantini A, Grippo A, Fossi S, Cesaretti C, Piccioli A, Peris A, et al. Prediction of 'awakening' and outcome in prolonged acute coma from severe traumatic head injury: evidence for validity of short latency SEPs. Clin Neurophysiol. 2005;116:229–35.
41. Houlden DA, Taylor AB, Feinstein A, Midha R, Bethune AJ, Stewart CP, et al. Early somatosensory evoked potential grades in comatose traumatic brain injury patients predict cognitive and functional outcome. Crit Care Med. 2010;38:167–74.
42. Daltrozzo J, Wioland N, Mutschler V, Kotchoubey B. Predicting coma and other low responsive patients outcome using event related brain potentials: a meta-analysis. Clin Neurophysiol. 2007;118:606–14.
43. Fischer C, Luauté J, Némoz C, Morlet D, Kirkorian G, Mauguière F. Improved prediction of awakening or nonawakening from severe anoxic coma using tree-based classification analysis. Crit Care Med. 2006;34:1520–4.
44. Luauté J, Fischer C, Adeleine P, Morlet D, Tell L, Boisson D. Late auditory and event-related potentials can be useful to predict good functional outcome after coma. Arch Phys Med Rehabil. 2005;86:917–23.
45. Whyte J, Katz D, Long D, DiPasquale MC, Polansky M, Kalmar K, et al. Predictors of outcome in prolonged posttraumatic disorders of consciousness and assessment of medication effects: a multicenter study. Arch Phys Med Rehabil. 2005;86:453–62.
46. Xu W, Jiang G, Chen Y, Wang X, Jiang X. Prediction of minimally conscious state with somatosensory evoked potentials in long-term unconscious patients after traumatic brain injury. J Trauma Acute Care Surg. 2012;72:1024–9.

47. Cavinato M, Freo U, Ori C, Zorzi M, Tonin P, Piccione F, Merico A. Post-acute P300 predicts recovery of consciousness from traumatic vegetative state. Brain Inj. 2009;23:973–80.
48. Qin P, Wu X, Huang Z, Duncan NW, Tang W, Wolff A, et al. How are different neural networks related to consciousness? Ann Neurol. 2015;78:594–605.
49. Boccagni C, Bagnato S, Sant'Angelo A, Prestandrea C, Galardi G. Usefulness of standard EEG in predicting the outcome of patients with disorders of consciousness after anoxic coma. J Clin Neurophysiol. 2011;28:489–92.
50. Estraneo A, Moretta P, Loreto V, Lanzillo B, Cozzolino A, Saltalamacchia A, et al. Predictors of recovery of responsiveness in prolonged anoxic vegetative state. Neurology. 2013;80:464–70.
51. Hildebrandt H, Happe S, Deutschmann A, Basar-Eroglu C, Eling P, Brunhöber J. Brain perfusion and VEP reactivity in occipital and parietal areas are associated to recovery from hypoxic vegetative state. J Neurol Sci. 2007;260:150–8.
52. Dolce G, Quintieri M, Serra S, Lagani V, Pignolo L. Clinical signs and early prognosis in vegetative state: a decisional tree, data-mining study. Brain Inj. 2008;22:617–23.
53. Whyte J, Gosseries O, Chervoneva I, DiPasquale MC, Giacino J, Kalmar K, et al. Predictors of short-term outcome in brain-injured patients with disorders of consciousness. Prog Brain Res. 2009;177:63–72. doi:10.1016/S0079-6123(09)17706-3.
54. Weiss N, Tadie JM, Faugeras F, Diehl JL, Fagon JY, Guerot E. Can fast-component of nystagmus on caloric vestibulo-ocular responses predict emergence from vegetative state in ICU? J Neurol. 2012;259:70–6.
55. Babiloni C, Sarà M, Vecchio F, Pistoia F, Sebastiano F, Onorati P, et al. Cortical sources of resting-state alpha rhythms are abnormal in persistent vegetative state patients. Clin Neurophysiol. 2009;120:719–29.
56. Bagnato S, Boccagni C, Prestandrea C, Sant'Angelo A, Castiglione A, Galardi G. Prognostic value of standard EEG in traumatic and non-traumatic disorders of consciousness following coma. Clin Neurophysiol. 2010;121:274–80.
57. Logi F, Pasqualetti P, Tomaiuolo F. Predict recovery of consciousness in post-acute severe brain injury: the role of EEG reactivity. Brain Inj. 2011;25(10):972–9.
58. Sarà M, Pistoia F, Pasqualetti P, Sebastiano F, Onorati P, Rossini PM. Functional isolation within the cerebral cortex in the vegetative state: a nonlinear method to predict clinical outcomes. Neurorehabil Neural Repair. 2011;25:35–42. doi:10.1177/1545968310378508.
59. Fingelkurts AA, Fingelkurts AA, Bagnato S, Boccagni C, Galardi G. Prognostic value of resting-state electroencephalography structure in disentangling vegetative and minimally conscious states: a preliminary study. Neurorehabil Neural Repair. 2013;27:345–54.
60. Rosanova M, Gosseries O, Casarotto S, Boly M, Casali AG, Bruno MA, et al. Recovery of cortical effective connectivity and recovery of consciousness in vegetative patients. Brain. 2012;135:1308–20. doi:10.1093/brain/awr340.
61. Kang XG, Li L, Wei D, Xu XX, Zhao R, Jing YY, et al. Development of a simple score to predict outcome for unresponsive wakefulness syndrome. Crit Care. 2014;18:R37.
62. Bagnato S, Boccagni C, Sant'Angelo A, Prestandrea C, Mazzilli R, Galardi G. EEG predictors of outcome in patients with disorders of consciousness admitted for intensive rehabilitation. Clin Neurophysiol. 2015;126:959–66.
63. Schorr B, Schlee W, Arndt M, Bender A. Coherence in resting-state EEG as a predictor for the recovery from unresponsive wakefulness syndrome. J Neurol. 2016;263:937–53.
64. Kotchoubey B, Lang S, Mezger G, Schmalohr D, Schneck M, Semmler A, et al. Information processing in severe disorders of consciousness: vegetative state and minimally conscious state. Clin Neurophysiol. 2005;116:2441–53.
65. Wijnen VJ, van Boxtel GJ, Eilander HJ, de Gelder B. Mismatch negativity predicts recovery from the vegetative state. Clin Neurophysiol. 2007;118:597–605.
66. Qin P, Di H, Yan X, Yu S, Yu D, Laureys S, et al. Mismatch negativity to the patient's own name in chronic disorders of consciousness. Neurosci Lett. 2008;448:24–8.
67. Steppacher I, Eickhoff S, Jordanov T, Kaps M, Witzke W, Kissler J. N400 predicts recovery from disorders of consciousness. Ann Neurol. 2013;73:594–602.

68. Rohaut B, Faugeras F, Chausson N, King JR, Karoui IE, Cohen L, et al. Probing ERP correlates of verbal semantic processing in patients with impaired consciousness. Neuropsychologia. 2015;66:279–92.
69. Li R, Song WQ, Du JB, Huo S, Shan GX. Connecting the P300 to the diagnosis and prognosis of unconscious patients. Neural Regen Res. 2015;10:473–80.
70. Di H, Boly M, Weng X, Ledoux D, Laureys S. Neuroimaging activation studies in the vegetative state: predictors of recovery? Clin Med. 2008;8:502–7.
71. Coleman MR, Davis MH, Rodd JM, Robson T, Ali A, Owen AM, et al. Towards the routine use of brain imaging to aid the clinical diagnosis of disorders of consciousness. Brain. 2009;132:2541–52.
72. Vogel D, Markl A, Yu T, Kotchoubey B, Lang S, Müller F. Can mental imagery functional magnetic resonance imaging predict recovery in patients with disorders of consciousness? Arch Phys Med Rehabil. 2013;94:1891–8.
73. Stender J, Gosseries O, Bruno MA, Charland-Verville V, Vanhaudenhuyse A, Demertzi A, et al. Diagnostic precision of PET imaging and functional MRI in disorders of consciousness: a clinical validation study. Lancet. 2014;384:514–22.
74. Li L, Kang XG, Qi S, Xu XX, Xiong LZ, Zhao G, et al. Brain response to thermal stimulation predicts outcome of patients with chronic disorders of consciousness. Clin Neurophysiol. 2015;126:1539–47.
75. Wang F, Di H, Hu X, Jing S, Thibaut A, Di Perri C, et al. Cerebral response to subject's own name showed high prognostic value in traumatic vegetative state. BMC Med. 2015;13:83.
76. Wu X, Zou Q, Hu J, Tang W, Mao Y, Gao L, et al. Intrinsic functional connectivity patterns predict consciousness level and recovery outcome in acquired brain injury. J Neurosci. 2015;35:12932–46.
77. Gouvier WD, Blanton PD, LaPorte KK, Nepomuceno C. Reliability and validity of the Disability Rating Scale and the Levels of Cognitive Functioning scale in monitoring recovery from severe head injury. Arch Phys Med Rehabil. 1987;68:94–7.
78. Wilson JT, Pettigrew LE, Teasdale GM. Structured interviews for the GOS and the GOS-E: guidelines for daily use. J Neurotrauma. 1998;15:573–85.
79. Boly M, Faymonville ME, Peigneux P, Lambermont B, Damas P, Del Fiore G, et al. Auditory processing in severely brain injured patients: differences between the minimally conscious state and the persistent vegetative state. Arch Neurol. 2004;61:233–8.
80. Azabou E, Fischer C, Mauguiere F, Vaugier I, Annane D, Sharshar T, et al. Prospective Cohort Study evaluating the prognostic value of simple EEG parameters in Postanoxic Coma. Clin EEG Neurosci. 2016;47:75–82.
81. Kang XG, Yang F, Li W, Ma C, Li L, Jiang W. Predictive value of EEG-awakening for behavioral awakening from coma. Ann Intensive Care. 2015;5:52.
82. Synek VM. Prognostically important EEG coma patterns in diffuse anoxic and traumatic encephalopathies in adults. J Clin Neurophysiol. 1988;5:161–74.
83. Edlow BL, Giacino JT, Wu O. Functional MRI and outcome in traumatic coma. Curr Neurol Neurosci Rep. 2013;13:375. doi:10.1007/s11910-013-0375-y.
84. Raichle ME, MacLeod AM, Snyder AZ, Powers WJ, Gusnard DA, Shulman GL. A default mode of brain function. Proc Natl Acad Sci U S A. 2001;98:676–82.
85. Whyte J, Nordenbo AM, Kalmar K, Merges B, Bagiella E, Chang H, et al. Medical complications during inpatient rehabilitation among patients with traumatic disorders of consciousness. Arch Phys Med Rehabil. 2013;94:1877–83.
86. Ganesh S, Guernon A, Chalcraft L, Harton B, Smith B, Louise-Bender PT. Medical comorbidities in disorders of consciousness patients and their association with functional outcomes. Arch Phys Med Rehabil. 2013;94:1899–907.
87. Pistoia F, Sacco S, Franceschini M, Sarà M, Pistarini C, Cazzulani B, Simonelli I, Pasqualetti P, Carolei A. Comorbidities: a key issue in patients with disorders of consciousness. J Neurotrauma. 2015;32:682–8. doi:10.1089/neu.2014.3659.
88. Pascarella A, Trojano L, Loreto V, Bilo L, Moretta P, Estraneo A. Long-term outcome of patients with disorders of consciousness with and without epileptiform activity and seizures: a prospective single centre cohort study. J Neurol. 2016;263:2048–56. doi:10.1007/s00415-016-8232-y.

Chapter 3
Linking Complex Alterations in Functional Network Connectivity to Disorders of Consciousness

Julia S. Crone and Martin M. Monti

Abstract In the last decade, research has focused on finding neural correlates of consciousness for diagnosis and prognosis after severe brain injury using neuroimaging studies. Because patients with disorders of consciousness are not or only limitedly capable of following instructions, studies investigating resting-state connectivity have been a focus of interest. This chapter gives an overview of the research on functional network connectivity in disorders of consciousness and common methods used to investigate these alterations such as independent component analysis, seed-based approaches, graph theory, and spectral dynamic causal modeling. Research demonstrates that properties of resting-state networks may provide further evidence for diagnosis and prognosis but also show limitations in interpretability. In addition, the existence of so-called hot zones of neuronal correlates of consciousness is discussed. In the second half of this chapter, we outline the caveats of resting-state functional imaging in severe brain injury. Motion, artifacts, normalization procedures, and interpretability pose serious obstacles when analyzing resting-state connectivity particularly in the injured brain. Nevertheless, resting-state connectivity analyses are a powerful tool to investigate patients with disorders of consciousness.

J.S. Crone, Ph.D. (✉)
Department of Psychology, University of California Los Angeles, Los Angeles, CA 90095, USA
e-mail: j.crone@neurocognition.org

M.M. Monti, Ph.D.
Department of Psychology, University of California Los Angeles, Los Angeles, CA 90095, USA

Department of Neurosurgery, David Geffen School of Medicine at UCLA, Brain Injury Research Center (BIRC), Los Angeles, CA 90095, USA

C. Schnakers, S. Laureys (eds.), *Coma and Disorders of Consciousness*,
DOI 10.1007/978-3-319-55964-3_3

Disorders of consciousness can be caused by severe brain injury and affect profoundly the structural and functional integrity of the brain's core architecture. Understanding the complexity of this architecture is the main challenge when linking brain function to cognitive deficits such as impaired consciousness. Neuroimaging in these patients has become a state-of-the-art tool to gain deeper insight into the functional and structural changes underlying their deficits and, more in general, the neuronal correlates of consciousness. The early investigations using neuroimaging in patients with disorders of consciousness revealed major alterations in brain connectivity [1–3]. The focus of these early studies was to find additional and more reliable diagnostic measures bearing in mind a lack of accuracy in the standard clinical assessment of their cognitive abilities [4] (see Chap. 1). To accomplish this goal, functional and structural characteristics of the brain are compared between different levels of impairment (ranging from coma, vegetative state, to the minimally conscious state) to uncover associations between the underlying degree of cognitive deficits and alterations in brain functioning.

In the past 10 years, functional connectivity during resting state has become a particularly promising perspective for research in severe brain injury and impaired consciousness. Resting-state imaging has the great advantage of not involving task-related sensory input or behavioral output, which can be impaired by the specific nature of the brain injury and potentially mask the presence of (minimal) consciousness. Since the focus of interest lies on alterations in the basic brain functioning of patients with disorders of consciousness, rather than on specific deficits in higher-level cognitive domains, there is also no need to trigger these cognitive processes with specific tasks. Another reason for studying the resting state in patients is that without controlling the cognitive processes during task performance (which is impossible in unresponsive patients), task-specific stimuli may generate similar brain states independent of the patient's level of consciousness [5]. During resting state, fluctuations are observed in the blood oxygen level-dependent (BOLD) signal while performing functional magnetic resonance imaging (fMRI). These fluctuations show an organized pattern of functionality throughout the brain and are associated with cognitive functioning [6].

Alterations of Brain Networks in Disorders of Consciousness

At rest, fluctuations in the BOLD signal of different brain regions are synchronized forming distinct networks throughout the brain [7, 8]. The most paradigmatic resting-state network, the so-called default mode network, connects the medial frontal cortex, medial posterior cortex, and temporoparietal regions [9] (see Fig. 3.1). A key characteristic of the default mode network is its activation during rest and deactivation during performance of various attention-demanding cognitive tasks [10–12]. It has been speculated that the BOLD fluctuations establishing the default mode network are related to conscious cognition [13], mind wandering [14], or internal reflection [9, 15] and that its deactivation reflects interruptions of

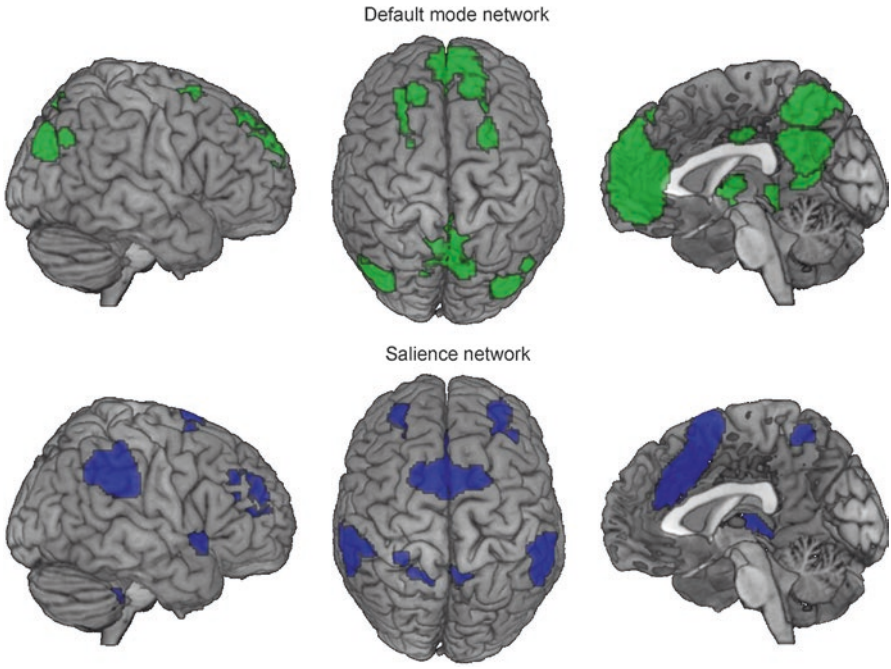

Fig. 3.1 Examples of resting-state networks as defined here [22]. *Top* (*green*): default mode network. *Bottom* (*blue*): salience network

introspective processing enabling attention-demanding actions [12, 16]. Supporting the latter speculations, this network is active rather than depressed during tasks involved in internal-directed cognition such as autobiographical memory, imagery spatial navigation, and theory of mind as demonstrated by a meta-analysis [17]. Single components of the default mode network are affected in different ways depending on the properties of the task such as emotional or self-referring features. But as a whole, the default mode network seems to play an enhanced role in attention focusing [18]. Nevertheless, the exchange of information within the default mode network is never turned off completely but rather adjusted at a fine-grained level as studies in sleep [19], in light sedation [20], as well as in deeply anesthetized monkeys [21] demonstrate.

In addition, the default mode network has been shown to be anticorrelated with other resting-state networks such as the dorsal attention network [10]. However, when studying local cell recordings in the cat brain across time, these anticorrelations are only present about 20% of the time, while 80% of the time, the two networks seem to cooperate depending on the state of mind [18].

The most common methods to study the default mode network are independent component analysis [23] and seed-based approaches [8]. While the independent component analysis is data-driven, the seed-based correlation analysis depends on spatial assumptions and regions of interest. Independent component analysis

attempts to separate a multivariate signal in (spatial) independent sources resulting in several independent connectivity maps of the brain. For the seed-based approach, connectivity depends on the time series of a selected seed region and its correlation with the time series of all other voxels. It is also possible to explore properties of resting-state networks using structural information such as probabilistic tractography, a diffusion tensor imaging method used to identify anatomical connections based on the molecular diffusion process in tissues in three-dimensional space.

The involvement of the default mode network in self- and attention-related tasks and its prominent occurrence has led researchers to investigate its alterations in disorders of consciousness. Studies demonstrate reduced functional connectivity within the default mode network in patients [24–29] and functional [30, 31] as well as structural [32] correlation with the level of behavioral responsiveness as measured by the Coma Recovery Scale-Revised [33] (see Chap. 1 for further detail on behavioral assessment). In addition, an intact default mode network was observed in comatose patients who eventually recovered consciousness but not in patients who did not awake from coma. This finding indicates that connectivity of the default mode network may have prognostic value for comatose patients [34]. A similar finding in patients in the vegetative state proposes that patients who do not emerge show reduced connectivity between regions within the default mode network compared to patients who regain consciousness [35]. Another link to the level of impairment has been found when investigating deactivation of the default mode network in response to language [36]. Only those patients who showed preserved responses to language in higher-cortical areas were able to interrupt ongoing mental processes to focus attention, that is, demonstrate a local decrease in BOLD activity.

The default mode network may be the most paradigmatic resting-state network, but it is not the only to be altered in disorders of consciousness. Differences in connectivity strength between patient groups have been shown also in the salience network [35] (see Fig. 3.1). When discriminating the impairment of various resting-state networks such as the default mode, frontoparietal, salience, auditory, visual, and sensorimotor in patients using a machine learning approach [37], functional connectivity in all networks showed a correlation with the level of behavioral responsiveness and a high discriminative capacity for separating patients according to their severity of impairment. As of a note, this finding could not be confirmed in a study investigating the specificity and sensitivity of the mere presence of various resting-state networks [29] which may be due to the fact that the default mode network was the only network identified in all subjects.

Another exciting approach to explore network properties of the brain is graph-theoretical techniques [38]. Graph theory is the study of mathematical structures used to model relations between objects and has been applied in all kinds of fields such as computer science, chemistry, physics, biology, economics, and sociology. In graph theory, complex networks are defined as a set of nodes connected by edges. Their constellation is described by network metrics. Clusters of functionally associated areas show a high density of local connections with few connections between

functionally segregated clusters [39, 40]. This small-world constellation ensures a high efficiency in information processing at a relatively low cost of wiring length [41]. These properties give rise to, for instance, the necessary balance to maintain a high level of cognition [42] between information segregation (as a capacity for specialized processing within densely interconnected brain regions) and integration (as a capacity to combine the specialized processing from segregated brain regions). Graph-theoretical approaches provide a perfect source to study the topological arrangement of functional communication and structural organization using metrics such as degree (number of edges of each node), clustering (degree to which the node's neighbors are also neighbors of each other), and efficiency (quantification of its robustness to failure).

Recent investigations applying graph-theoretical measures in disorders of consciousness demonstrate preserved small-world properties of the overall organization of the brain's network despite severe alterations [43–45]. For instance, comatose patients show critical impairment at the local level of network organization but no global alterations [43]. In contrast, when comparing minimal conscious state, vegetative state, and healthy controls, the balance between segregation and integration in both patient groups is globally affected as well. Another study compared the scale-free properties between propofol-induced loss of consciousness and the vegetative state [45]. Scale-free networks are characterized by high robustness to failure because of their highly heterogeneous degree distribution. The vast majority of nodes are connected to only a few other nodes with a tiny minority of actual hubs (nodes that are disproportional highly connected to other nodes). Therefore, the likelihood that randomly occurring failure affects a highly connected hub (and thus is fatal) is almost negligible. Interestingly, the deeply sedated brain demonstrates scale-free properties, while the vegetative state does not [45].

At a more local level, topological measures such as degree, efficiency, and clustering are reduced in patients in medial posterior regions [43, 44], while in frontal regions, findings depart depending on the study and patient population. In minimal conscious state and vegetative state, an increase in lateral frontal and a decrease in medial frontal regions have been detected [44]. In comatose patients, however, there was an increase in medial frontal regions [43]. In addition, the degree of segregation differs between vegetative state and minimal conscious state in medial parietal and is related to behavioral responsiveness in frontal regions.

Recently, a new method for resting-state fMRI data, spectral dynamic causal modeling [46], has been validated allowing to investigate alterations in the causal interaction of resting-state networks. Applying this approach to explore the effective connectivity within the default mode network revealed that the posterior cingulate cortex functions as the main driven hub in healthy subjects [47]. In patients with disorders of consciousness, disruption regarding self-inhibition and neuronal oscillations in the posterior cingulate cortex is a key aspect linking alterations in consciousness after severe brain injury to the intrinsic functional architecture of the default mode network [47].

A Hot Zone of Neuronal Correlates of Consciousness?

In contrast to the recent findings reported above, there has been a long history of research on connectivity between the thalamus and the frontal cortex in disorders of consciousness. An initial study in one patient recovering consciousness after traumatic brain injury [48] (together with evidence from the animal model [49, 50] and from experimental manipulations testing conscious awareness of stimuli in healthy subjects [51–53]) highlights the role of thalamo-frontal connectivity in disorders of consciousness. The thalamus is highly reciprocal connected with cortical areas, especially with frontal regions. This theoretically makes the thalamus a perfect candidate for integrating information computed by cortical areas and therefore generating conscious awareness. However, the critical involvement of the thalamus for consciousness has not been confirmed. Recent evidence rather suggests a less prominent role of the thalamus in disorders of consciousness after traumatic brain injury. While the structural atrophy of the thalamus is related to motor function as well as communication, there is no relation with the level of arousal or overall conscious responsiveness in patients [54]. Studies investigating functional connectivity did not find significant correlations with the overall level of conscious responsiveness and thalamo-cortical connectivity in patients [3, 44]. This would be in line with evidence from studies investigating propofol- or sleep-induced loss of consciousness and demonstrating a rather secondary role of thalamo-cortical connectivity [55–59]. It is more likely that thalamo-cortical connectivity is crucial for effective cortical communication providing higher-order cognition and control of motor function [60].

Obviously, a much more consistent finding in patients with disorders of consciousness is alterations of the medial posterior regions. The posterior cingulate cortex with the adjacent precuneus is the most prominent part of the default mode network. The posterior cingulate cortex is not only sensitive to the state of arousal but serves as a complex control mechanism in respect to the breadth of attention (focused vs. broadly alert) and its direction (internally vs. externally) [61]. It is also part of the so-called rich club referring to brain regions with much higher interconnectivity throughout the brain than others which are suggested to play a critical role in overall brain communication by enabling highly efficient information integration [62]. The posterior cingulate cortex shows a complex pattern of interaction with different functional connectivity networks emphasizing a multifaceted role in global brain communication [63, 64]. This makes the posterior cingulate cortex as part of the default mode network to a major transit hub for exchange of information throughout the whole brain [65–68]. In disorders of consciousness, connectivity of medial posterior regions during resting state is found to be altered in all relevant studies often distinguishing between vegetative state and minimal conscious state patients [30, 44, 69, 70]. Based on these observations, Koch and coworkers plead for a temporo-parietal-occipital *hot zone* of neuronal correlates of consciousness [71]. Indeed, findings from fMRI studies make it tempting to speculate about the causal association between medial posterior regions and impaired consciousness

especially because specific hubs in the brain—if impaired—have fatal effects for the overall communication due to its structural organization as a scale-free network. However, precaution is required when drawing conclusion regarding the causal involvement of changes in the regional activity of the blood oxygen level-dependent (BOLD) signal in the severely damaged brain.

Caveats of Resting-State Functional Imaging in Severe Brain Injury

It is important to be mindful of the methodological and conceptual limitations that arise from functional connectivity studies investigating consciousness and severe brain injury when discussing the findings.

Motion and Artifacts

Acquiring, analyzing, and interpreting resting-state fMRI data in the severely damaged brain is more than challenging. Motion is the most problematic but also the most considered disadvantage when working with resting-state fMRI data in patients with disorders of consciousness. Patients in the vegetative state and especially in the minimally conscious state can exhibit high rates of spontaneous motion. To make things even more problematic, the correlation between motion and the level of recovery follows a u-shaped curve. Patients in the minimal state typically show more motion than patients in the vegetative state. In recovered patients, however, the trend is the opposite: with less motion, the better the recovery.

Motion artifacts in functional connectivity analyses are known to be highly problematic [72–76]. The effects are complex and may depend on the specific acquisition and analysis procedure chosen. Small head movements may produce spurious but organized effects on the BOLD signal which leads to false distance-dependent correlations. This problem is not trivial when the question of interest is correlated with the amount of motion, that is, when comparing high-motion groups with low-motion groups. Consequently, differences between vegetative state and minimal conscious state as well as between minimal conscious state and control groups may be completely due to differences in head motion. In addition, motion affects nearby voxels more than distant ones which has severe impact on the properties of networks such as long-distance vs. short-distance connectivity, efficiency, and clustering measures. This highly affects findings beyond the mere comparison of group differences. The awareness of these problematic issues has just arisen and denoising strategies are still evolving. Most of the functional connectivity studies which are reported in this chapter have not implemented sufficient approaches to control for motion artifacts.

A similar issue is the brain injuries themselves. Lesions can produce spurious artifacts which affect the variance of the BOLD signal in surrounding areas of interest. The severity of the lesions tends to correlate with the level of impaired consciousness and cognition, that is, vegetative state patients typically have a greater level of brain damage than minimal conscious state patients.

Normalization and Selection of Region of Interest

Less commonly discussed but definitely as delicate to deal with is the normalization procedure and selection of regions of interest in patients with severe traumatic brain injury. Commonly, the functional images acquired are automatically transferred into some sort of common referential space, such as the Montreal Neurological Institute (MNI) space, to conduct group comparisons. This is usually done for region of interest analyses such as graph-theoretical approaches or effective connectivity analyses and data-driven approaches at the group level such as independent component analysis likewise. To define a region of interest, the coordinates are identified in one common standard space and then applied to all subjects in the same space. This way it is ensured that the comparison of changes in the BOLD signal of a particular area in the brain is the same across subjects. For patients with severe brain lesions, however, there is no adequate solution for an automatic procedure of normalization into standard space [77–79]. The best but still not flawless method is cost function masking proposed by Brett et al. [80]. However, this process is not only very time consuming but, especially in brains with widespread and diffuse lesions, difficult to perform because it requires the manual tracing of the lesion borders.

In addition, the process of normalization as a purpose of defining common brain regions of interest does also not account for plasticity and adaptation of neighboring regions assimilating functions of lesioned parts.

An alternative approach in these patients is to process the data in single-subject space and define regions of interest functionally at the individual level if applicable. However, most of the studies performed in patients with disorders of consciousness used an automatic normalization procedure and coordinates in standard space to define regions of interest.

Aspects of Interpretability When Using Functional Neuroimaging in Disorders of Consciousness

Besides the specific methodological caveats of data preprocessing, the interpretability of findings is complicated for fMRI data in general but in disorders of consciousness particularly. The BOLD signal originates from changes in the deoxyhemoglobin concentration meaning it is sensitive to changes in cerebral blood flow, blood volume, and tissue oxygen consumption. Consequently, the measured BOLD response is dependent on the size and orientation of and the distance to the blood vessel. Intravascular

and extravascular water have also different influences on the BOLD signal, and these influences depend on the parameter settings during data acquisition. For simple connectivity analyses in which the time series of one region is compared to the time series of another, the challenge of modeling the BOLD response appropriately is not of such importance. However, when it comes to the interpretation of differences in connectivity between compared groups or the interpretation of an association with behavioral assessment, these factors are indeed significant.

This multifaceted interaction gets even more complicated when dealing with severe brain injury. In the healthy brain, neuronal activity typically evokes a concurrent increase in oxygen consumption, blood flow, and volume. Astrocytes and pericytes, non-neuronal brain cells, are highly involved in regulation of vasodilatory responses [81, 82] and thus a crucial element of the BOLD signal. Especially pericytes are significantly affected by impaired arterial blood supply such as in ischemia or traumatic brain injury. As a consequence, alteration of the BOLD signal in traumatic brain injury may rather mark the prolonged death of pericytes than impaired neuronal activity. However, the exact interaction between mechanisms caused by severe brain injury and its effects on the BOLD signal are unknown. This is exacerbated by the fact that alterations in structural connectivity are not directly related to functional connectivity. From simulations we know that changes in brain connectivity have widespread, complex effects on functional connectivity and are not restricted to local changes [42, 66, 83]. Straightforward interpretation of these alterations is illusive. For instance, increases in functional connectivity do not always go along with a strength in structural connectivity and cannot be entirely related, for example, to compensatory processes reflected by neural plasticity [83, 84].

Another complicating factor for interpretation we have to be aware of is that neuronal mechanisms identified with neuroimaging techniques do not necessarily reflect neuronal correlates of consciousness [85, 86]. Mechanisms identified and related to the level of consciousness in patients do not exclusively reveal its neuronal correlates but could rather be prerequisites for or consequences of conscious experience. In healthy subjects, an empirical distinction of these different brain processes is already a huge challenge that has not been resolved to a satisfactory extent so far. For patients with severe brain injury, however, this is even more challenging due to the earlier mentioned possible confounds.

It remains a challenge to specify the cause of changes in functional connectivity in the diseased brain and disentangle injury-specific influences on the BOLD signal from underlying structural and functional changes, or actual changes in cognitive function.

Conclusion

Despite the general lack of awareness for conscientious interpretability of fMRI findings and the problematic aspects of data preprocessing, resting-state fMRI analyses in disorders of consciousness offer a unique insight into very specific alterations of the brain's network mechanisms that other methods cannot

provide. This approach enables the identification of impairments at the macroscale level by shifting the spotlight on mechanisms of interaction that emerge exclusively at this broaden scale. Previous research in disorders of consciousness has shown that functional connectivity is fundamentally reorganized and that affected hot zones such as medial parietal regions play a critical role for consciousness and cognition.

In combination with other methods and cautious interpretation, resting-state fMRI and functional connectivity analyses are a crucial part of investigating disorders of consciousness and enhance our knowledge of the brain mechanisms underlying impaired consciousness.

References

1. Laureys S, Lemaire C, Maquet P, Phillips C, Franck G. Cerebral metabolism during vegetative state and after recovery to consciousness. J Neurol Neurosurg Psychiatry. 1999;67(1):121.
2. Laureys S, Goldman S, Phillips C, Van Bogaert P, Aerts J, Luxen A, et al. Impaired effective cortical connectivity in vegetative state: preliminary investigation using PET. Neuroimage. 1999;9(4):377–82.
3. Laureys S, Faymonville ME, Peigneux P, Damas P, Lambermont B, Del Fiore G, et al. Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. Neuroimage. 2002;17(2):732–41.
4. Owen AM, Menon DK, Johnsrude IS, Bor D, Scott SK, Manly T, et al. Detecting residual cognitive function in persistent vegetative state. Neurocase. 2002;8(5):394–403.
5. Crone JS, Höller Y, Bergmann J, Golaszewski S, Trinka E, Kronbichler M. Self-related processing and deactivation of cortical midline regions in disorders of consciousness. Front Hum Neurosci. 2013;7:504.
6. Biswal B, Yetkin FZ, Haughton VM, Hyde JS. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med. 1995;34(4):537–41.
7. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci. 2007;8(9):700–11.
8. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci U S A. 2003;100(1):253–8.
9. Raichle ME, Snyder AZ. A default mode of brain function: a brief history of an evolving idea. Neuroimage. 2007;37(4):1083–90.
10. Fox MD, Snyder AZ, Vincent JL, Corbetta M, Van EDC, Raichle ME. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A. 2005;102(27):9673–8.
11. Shulman GL, Fiez JA, Corbetta M, Buckner RL, Miezin FM, Raichle ME, et al. Common blood flow changes across visual tasks: II. Decreases in cerebral cortex. J Cogn Neurosci. 1997;9(5):648–63.
12. Gusnard DA, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. Nat Rev Neurosci. 2001;2(10):685–94.
13. Morcom AM, Fletcher PC. Does the brain have a baseline? Why we should be resisting a rest. Neuroimage. 2007;37(4):1073–82.
14. Andrews-Hanna JR, Reidler JS, Huang C, Buckner RL. Evidence for the default network's role in spontaneous cognition. J Neurophysiol. 2010;104(1):322–35.
15. Mason MF, Norton MI, Van Horn JD, Wegner DM, Grafton ST, Macrae CN. Wandering minds: the default network and stimulus-independent thought. Science. 2007;315(5810):393–5.

16. Binder JR. Task-induced deactivation and the “resting” state. Neuroimage. 2012;62(2): 1086–91.
17. Spreng RN, Mar RA, Kim AS. The common neural basis of autobiographical memory, prospection, navigation, theory of mind, and the default mode: a quantitative meta-analysis. J Cogn Neurosci. 2009;21(3):489–510.
18. Popa D, Popescu AT, Paré D. Contrasting activity profile of two distributed cortical networks as a function of attentional demands. J Neurosci. 2009;29(4):1191–201.
19. Horovitz SG, Fukunaga M, de Zwart JA, van Gelderen P, Fulton SC, Balkin TJ, et al. Low frequency BOLD fluctuations during resting wakefulness and light sleep: a simultaneous EEG-fMRI study. Hum Brain Mapp. 2008;29(6):671–82.
20. Greicius MD, Kiviniemi V, Tervonen O, Vainionpää V, Alahuhta S, Reiss AL, et al. Persistent default-mode network connectivity during light sedation. Hum Brain Mapp. 2008;29(7): 839–47.
21. Vincent JL, Patel GH, Fox MD, Snyder AZ, Baker JT, Van Essen DC, et al. Intrinsic functional architecture in the anaesthetized monkey brain. Nature. 2007;447(7140):83–6.
22. Shirer WR, Ryali S, Rykhlevskaia E, Menon V, Greicius MD. Decoding subject-driven cognitive states with whole-brain connectivity patterns. Cereb Cortex. 2012;22(1):158–65.
23. Beckmann CF, DeLuca M, Devlin JT, Smith SM. Investigations into resting-state connectivity using independent component analysis. Philos Trans R Soc Lond B Biol Sci. 2005;360(1457): 1001–13.
24. Cauda F, Micon BM, Sacco K, Duca S, D’Agata F, Geminiani G, et al. Disrupted intrinsic functional connectivity in the vegetative state. J Neurol Neurosurg Psychiatry. 2009;80(4): 429–31.
25. Boly M, Tshibanda L, Vanhaudenhuyse A, Noirhomme Q, Schnakers C, Ledoux D, et al. Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient. Hum Brain Mapp. 2009;30(8):2393–400.
26. Soddu A, Vanhaudenhuyse A, Bahri MA, Bruno MA, Boly M, Demertzi A, et al. Identifying the default-mode component in spatial IC analyses of patients with disorders of consciousness. Hum Brain Mapp. 2012;33(4):778–96.
27. Demertzi A, Gómez F, Crone JS, Vanhaudenhuyse A, Tshibanda L, Noirhomme Q, et al. Multiple fMRI system-level baseline connectivity is disrupted in patients with consciousness alterations. Cortex. 2014;52:35–46.
28. Hannawi Y, Lindquist MA, Caffo BS, Sair HI, Stevens RD. Resting brain activity in disorders of consciousness: a systematic review and meta-analysis. Neurology. 2015;84(12):1272–80.
29. Roquet D, Foucher JR, Froehlig P, Renard F, Pottecher J, Besancenot H, et al. Resting-state networks distinguish locked-in from vegetative state patients. Neuroimage Clin. 2016;12:16–22.
30. Vanhaudenhuyse A, Noirhomme Q, Tshibanda LJ, Bruno MA, Boveroux P, Schnakers C, et al. Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. Brain. 2010;133(Pt 1):161–71.
31. Rosazza C, Andronache A, Sattin D, Bruzzone MG, Marotta G, Nigri A, et al. Multimodal study of default-mode network integrity in disorders of consciousness. Ann Neurol. 2016;79(5):841–853.
32. Fernández-Espejo D, Soddu A, Cruse D, Palacios EM, Junque C, Vanhaudenhuyse A, et al. A role for the default mode network in the bases of disorders of consciousness. Ann Neurol. 2012;72(3):335–43.
33. Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil. 2004;85(12):2020–9.
34. Norton L, Hutchison RM, Young GB, Lee DH, Sharpe MD, Mirsattari SM. Disruptions of functional connectivity in the default mode network of comatose patients. Neurology. 2012;78(3):175–81.
35. Qin P, Wu X, Huang Z, Duncan NW, Tang W, Wolff A, et al. How are different neural networks related to consciousness? Ann Neurol. 2015;78(4):594–605.
36. Crone JS, Ladurner G, Holler Y, Golaszewski S, Trinka E, Kronbichler M. Deactivation of the default mode network as a marker of impaired consciousness: an fMRI study. PLoS One. 2011;6(10):e26373.

37. Demertzi A, Antonopoulos G, Heine L, Voss HU, Crone JS, de Los Angeles C, et al. Intrinsic functional connectivity differentiates minimally conscious from unresponsive patients. Brain. 2015;138:2619–31.
38. Bondy JA, Murty USR. Graph theory with applications. London: Macmillan; 1976.
39. Achard S, Salvador R, Whitcher B, Suckling J, Bullmore E. A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. J Neurosci. 2006;26(1):63–72.
40. Salvador R, Suckling J, Coleman MR, Pickard JD, Menon D, Bullmore E. Neurophysiological architecture of functional magnetic resonance images of human brain. Cereb Cortex. 2005;15(9):1332–42.
41. Achard S, Bullmore E. Efficiency and cost of economical brain functional networks. PLoS Comput Biol. 2007;3(2):e17.
42. Honey CJ, Sporns O. Dynamical consequences of lesions in cortical networks. Hum Brain Mapp. 2008;29(7):802–9.
43. Achard S, Delon-Martin C, Vertes PE, Renard F, Schenck M, Schneider F, et al. Hubs of brain functional networks are radically reorganized in comatose patients. Proc Natl Acad Sci U S A. 2012;109:20608–13.
44. Crone JS, Soddu A, Holler Y, Vanhaudenhuyse A, Schurz M, Bergmann J, et al. Altered network properties of the fronto-parietal network and the thalamus in impaired consciousness. Neuroimage Clin. 2013;4:240–8.
45. Liu X, Ward BD, Binder JR, Li SJ, Hudetz AG. Scale-free functional connectivity of the brain is maintained in anesthetized healthy participants but not in patients with unresponsive wakefulness syndrome. PLoS One. 2014;9(3):e92182.
46. Friston KJ, Kahan J, Biswal B, Razi A. A DCM for resting state fMRI. Neuroimage. 2014;94:396–407.
47. Crone JS, Schurz M, Höller Y, Bergmann J, Monti M, Schmid E, et al. Impaired consciousness is linked to changes in effective connectivity of the posterior cingulate cortex within the default mode network. Neuroimage. 2015;110:101–9.
48. Laureys S, Faymonville ME, Luxen A, Lamy M, Franck G, Maquet P. Restoration of thalamocortical connectivity after recovery from persistent vegetative state. Lancet. 2000;355(9217):1790–1.
49. Baker R, Gent TC, Yang Q, Parker S, Vyssotski AL, Wisden W, et al. Altered activity in the central medial thalamus precedes changes in the neocortex during transitions into both sleep and propofol anesthesia. J Neurosci. 2014;34(40):13326–35.
50. Panagiotaropoulos TI, Kapoor V, Logothetis NK. Subjective visual perception: from local processing to emergent phenomena of brain activity. Philos Trans R Soc Lond B Biol Sci. 2014;369(1641):20130534.
51. Dehaene S, Changeux JP, Naccache L, Sackur J, Sergent C. Conscious, preconscious, and subliminal processing: a testable taxonomy. Trends Cogn Sci. 2006;10(5):204–11.
52. Dehaene S, Naccache L. Towards a cognitive neuroscience of consciousness: basic evidence and a workspace framework. Cognition. 2001;79(1–2):1–37.
53. Dehaene S, Naccache L, Cohen L, Bihan DL, Mangin JF, Poline JB, et al. Cerebral mechanisms of word masking and unconscious repetition priming. Nat Neurosci. 2001;4(7):752–8.
54. Lutkenhoff ES, Chiang J, Tshibanda L, Kamau E, Kirsch M, Pickard JD, et al. Thalamic and extrathalamic mechanisms of consciousness after severe brain injury. Ann Neurol. 2015;78:68–76.
55. Monti MM, Lutkenhoff ES, Rubinov M, Boveroux P, Vanhaudenhuyse A, Gosseries O, et al. Dynamic change of global and local information processing in propofol-induced loss and recovery of consciousness. PLoS Comput Biol. 2013;9(10):e1003271.
56. Boly M, Perlbarg V, Marrelec G, Schabus M, Laureys S, Doyon J, et al. Hierarchical clustering of brain activity during human nonrapid eye movement sleep. Proc Natl Acad Sci U S A. 2012;109(15):5856–61.

57. Silva A, Cardoso-Cruz H, Silva F, Galhardo V, Antunes L. Comparison of anesthetic depth indexes based on thalamocortical local field potentials in rats. Anesthesiology. 2010;112(2):355–63.
58. Mhuircheartaigh RN, Rosenorn-Lanng D, Wise R, Jbabdi S, Rogers R, Tracey I. Cortical and subcortical connectivity changes during decreasing levels of consciousness in humans: a functional magnetic resonance imaging study using propofol. J Neurosci. 2010;30(27):9095–102.
59. Fuller PM, Fuller P, Sherman D, Pedersen NP, Saper CB, Lu J. Reassessment of the structural basis of the ascending arousal system. J Comp Neurol. 2011;519(5):933–56.
60. Schiff ND. Recovery of consciousness after brain injury: a mesocircuit hypothesis. Trends Neurosci. 2010;33(1):1–9.
61. Leech R, Sharp DJ. The role of the posterior cingulate cortex in cognition and disease. Brain. 2014;137(Pt 1):12–32.
62. van den Heuvel MP, Sporns O. Rich-club organization of the human connectome. J Neurosci. 2011;31(44):15775–86.
63. Leech R, Braga R, Sharp DJ. Echoes of the brain within the posterior cingulate cortex. J Neurosci. 2012;32(1):215–22.
64. Leech R, Kamourieh S, Beckmann CF, Sharp DJ. Fractionating the default mode network: distinct contributions of the ventral and dorsal posterior cingulate cortex to cognitive control. J Neurosci. 2011;31(9):3217–24.
65. Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, et al. Mapping the structural core of human cerebral cortex. PLoS Biol. 2008;6(7):e159.
66. Honey CJ, Sporns O, Cammoun L, Gigandet X, Thiran JP, Meuli R, et al. Predicting human resting-state functional connectivity from structural connectivity. Proc Natl Acad Sci U S A. 2009;106(6):2035–40.
67. Deshpande G, Santhanam P, Hu X. Instantaneous and causal connectivity in resting state brain networks derived from functional MRI data. Neuroimage. 2011;54(2):1043–52.
68. Yan C, He Y. Driving and driven architectures of directed small-world human brain functional networks. PLoS One. 2011;6(8):e23460.
69. Crone JS, Soddu A, Höller Y, Vanhaudenhuyse A, Schurz M, Bergmann J, et al. Altered network properties of the fronto-parietal network and the thalamus in impaired consciousness. Neuroimage Clin. 2014;4:240–8.
70. Fernández-Espejo D, Junque C, Cruse D, Bernabeu M, Roig-Rovira T, Fábregas N, et al. Combination of diffusion tensor and functional magnetic resonance imaging during recovery from the vegetative state. BMC Neurol. 2010;10:77.
71. Koch C, Massimini M, Boly M, Tononi G. Neural correlates of consciousness: progress and problems. Nat Rev Neurosci. 2016;17(5):307–21.
72. Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. Neuroimage. 2012;59(3):2142–54.
73. Power JD, Cohen AL, Nelson SM, Wig GS, Barnes KA, Church JA, et al. Functional network organization of the human brain. Neuron. 2011;72(4):665–78.
74. Satterthwaite TD, Wolf DH, Loughead J, Ruparel K, Elliott MA, Hakonarson H, et al. Impact of in-scanner head motion on multiple measures of functional connectivity: relevance for studies of neurodevelopment in youth. Neuroimage. 2012;60(1):623–32.
75. Van Dijk KR, Sabuncu MR, Buckner RL. The influence of head motion on intrinsic functional connectivity MRI. Neuroimage. 2012;59(1):431–8.
76. Power JD, Schlaggar BL, Petersen SE. Recent progress and outstanding issues in motion correction in resting state fMRI. Neuroimage. 2015;105:536–51.
77. Andersen SM, Rapcsak SZ, Beeson PM. Cost function masking during normalization of brains with focal lesions: still a necessity? Neuroimage. 2010;53(1):78–84.
78. Ashburner J, Friston KJ. Unified segmentation. Neuroimage. 2005;26(3):839–51.

79. Crinion J, Ashburner J, Leff A, Brett M, Price C, Friston K. Spatial normalization of lesioned brains: performance evaluation and impact on fMRI analyses. Neuroimage. 2007;37(3): 866–75.
80. Brett M, Leff AP, Rorden C, Ashburner J. Spatial normalization of brain images with focal lesions using cost function masking. Neuroimage. 2001;14(2):486–500.
81. MacVicar BA, Newman EA. Astrocyte regulation of blood flow in the brain. Cold Spring Harb Perspect Biol. 2015;7(5). pii: a020388.
82. Hall CN, Reynell C, Gesslein B, Hamilton NB, Mishra A, Sutherland BA, et al. Capillary pericytes regulate cerebral blood flow in health and disease. Nature. 2014;508(7494):55–60.
83. Alstott J, Breakspear M, Hagmann P, Cammoun L, Sporns O. Modeling the impact of lesions in the human brain. PLoS Comput Biol. 2009;5(6):e1000408.
84. Kim J, Horwitz B. How well does structural equation modeling reveal abnormal brain anatomical connections? An fMRI simulation study. Neuroimage. 2009;45(4):1190–8.
85. Aru J, Bachmann T, Singer W, Melloni L. Distilling the neural correlates of consciousness. Neurosci Biobehav Rev. 2012;36(2):737–46.
86. de Graaf TA, Hsieh PJ, Sack AT. The 'correlates' in neural correlates of consciousness. Neurosci Biobehav Rev. 2012;36(1):191–7.

Chapter 4
Electrophysiology in Disorders of Consciousness: From Conventional EEG Visual Analysis to Brain-Computer Interfaces

C. Chatelle, D. Lesenfants, and Q. Noirhomme

Abstract Electroencephalography can offer many insights into brain activity useful for the study of disorders of consciousness. In this chapter, we will focus on the state of knowledge regarding the implementation of such a technique for diagnosis and prognosis in clinical setting, as well as the current effort for developing more reliable methods for assessing severely brain-injured patients with altered state of consciousness.

Electroencephalography

Electroencephalography is the measure of the brain's electrical activity using electrodes placed on the surface of the skull. It directly reflects neuronal activity with a high temporal resolution. However, the spatial resolution is poor for two main

C. Chatelle (✉)
Laboratory for NeuroImaging of Coma and Consciousness, Massachusetts General Hospital, Boston, MA, USA

Acute Neurorehabilitation Unit, Department of Clinical Neurosciences, University Hospital of Lausanne, Lausanne, Switzerland

Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium
e-mail: camillechatelle@gmail.com

D. Lesenfants
Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium

Laboratory for Neurorestorative Technology, School of Engineering, Brown University, Providence, RI, USA

Q. Noirhomme
Department of Cognitive Neuroscience, Maastricht University, Maastricht, The Netherlands

Brain Innovation B.V., Maastricht, The Netherlands

Cyclotron Research Centre, University of Liege, Liege, Belgium

C. Schnakers, S. Laureys (eds.), *Coma and Disorders of Consciousness*,
DOI 10.1007/978-3-319-55964-3_4

reasons: (1) it is limited by interelectrode distance, and (2) because of volume conduction, each sensor measures a sum of different brain sources; hence sensors have a correlated signal. The number of electrodes used depends on the application. For instance, when monitoring the level of anesthesia, only two electrodes are needed to obtain an electroencephalographic trace, while in clinical environments at least ten are used. In research, modern electrode caps have up to 256 electrodes. Electrode positioning on the cranial surface follows international nomenclatures (10-20 system for up to 19 electrodes and 10-10 system for more than 19 electrodes [1]), which aim to cover homogeneously most of the cranial surface. Electrodes are named according to their position on the scalp and have the letter F for frontal, C for central, P for parietal, O for occipital, or a letter combination such as FC for a position between frontal and central. Additionally, these letters are followed by a number (even for electrodes on the right hemisphere and odd for electrodes on the left hemisphere) or by the letter Z (for electrodes on the midline).

The measured signal results from a potential difference between two electrodes. It is, therefore, not possible to use only one electrode. There are two categories of montages: bipolar montages in which the electrodes are paired two by two and referential montages where all the electrodes are coupled to a single electrode called the reference. In a bipolar montage, it can be considered that the recorded signal stems from an imaginary position located between the two electrodes. In a referential montage, the reference should not be located in a region where a signal of interest has to be recorded. Common positions for the reference are the earlobes; the mastoids, possibly coupled; the nose; or a position on the midline. The choice of the reference electrode has an influence on the shape of the recorded signal, notably for evoked potentials. Bipolar montages are less sensitive to artifacts but will not detect events that are common to two coupled electrodes. A referential montage does not have this drawback but is, however, more sensitive to artifacts [2].

The electroencephalogram (EEG) does not only detect electrical fields generated by cerebral activity but also fields generated by muscular activity such as eye or eyelid movements or fields generated by electrical apparatus. Patients in altered states of consciousness are often surrounded by many different electronic equipment withstanding their vital functions. They have little control of their movements and can be spastic. Furthermore, they do not control their level of sudation, which can potentially be the cause of artifacts, which should be minimized during the recording. It is a good practice to simultaneously record respiration, heartbeats, and muscular activity in order to better track artifacts and eventually remove them from the signal. It is also important to have full knowledge of all drugs prescribed to the patient as some can have a sedative effect, which can result in a slower EEG, or others such as benzodiazepines can add additional fast frequencies to the signal. Some artifacts can be eliminated by data filtering. A notch filter removes the 50 Hz line noise (60 Hz in the United States and other regions in the world). The EEG spectrum covers frequencies ranging from less than 1 Hz to several hundreds of Hz. The use of filters should, therefore, depend on the frequency bands of interest. Too much filtering of low frequencies might hide slow-wave activity, while filtering high frequencies might hide spindles and spike waves. Heavy filtering results in a clean EEG trace but might remove some of the signal of interest [2]. Taking these

considerations into account, the EEG signal is often observed after filtering between 1 and 30 Hz, notably in sleep studies or for evoked potentials. These limits can then be adjusted in order to include more frequencies.

The electroencephalography (EEG) has a long history of use in the intensive care unit, and there is a well-documented literature on EEG abnormalities in comatose patients and patients in unresponsive wakefulness syndrome (UWS). Less is known about EEG activity in acute patients in minimally conscious state (MCS). The traditional visual inspection of the EEG is more and more complemented by event-related potentials. In parallel, researchers are developing new paradigms to probe higher and higher cognitive functions. New quantitative tools are developed to ease the interpretation of the EEG.

Clinical EEG

A routine clinical EEG recording usually lasts 20–30 min without stimulations to properly assess EEG background activity and to detect potential changes [3], and EEG reactivity should also be assessed, unless there is a concern of raised intracranial pressure due to stimuli [4]. Sufficient length of recording is necessary to ensure a reliable interpretation despite the presence of artifacts (e.g., electrode failure, movement or sweat artifacts) that could lead to undetectable physiological or even pathological events. The visual interpretation of an EEG trace gives information on the global cerebral activity of a patient.

Acute Stage

EEG Visual Analysis

In the acute stage, the EEG can help to establish the origin and the severity of the injury (e.g., in the case of a focal lesion or a diffuse dysfunction) and differentiate states that are symptomatically similar to coma such as an epileptic absence, a psychogenic coma, a noncooperative patient, or a locked-in syndrome (LIS). Combined with the etiology, the EEG can give an indication on the patient's prognosis. Finally, the EEG can track the patient evolution and the effect of drugs such as antiepileptics and sedative [3, 5, 6].

The EEG is useful for detecting and managing epileptic spikes, nonconvulsive epileptic seizures, or nonconvulsive status epilepticus [6]. Synchronized video recordings are strongly recommended as they provide useful information for identifying artifacts and getting further insights in case of seizure [7]. A nonconvulsive epileptic seizure does not present the usual signs of a complex partial seizure like oculomotor and masticatory muscle contraction, and the patient can appear confused, drowsy, or comatose. The EEG will show a continuous epileptic activity. Nonconvulsive seizures are present in 18–37% of patients in ICU [8, 9].

Management of epileptic activity is particularly challenging as delayed treatment of an ictal pattern may lead to difficulty in controlling a seizure or may result in further brain damage. Conversely, inappropriate use of antiepileptic drugs may lead to increased sedation, while overly aggressive treatment may result in complications due to side effect and pharmacokinetic interactions [10]. Furthermore, in acute comatose patients, the determination of truly epileptiform activity is also challenging. A patient with epileptic activity not responding to administered antiepileptic drugs and without possibility to treat the cause of the seizures has a poor prognosis [11].

Following a brain injury, whether it is of traumatic or anoxic origin, the EEG can be significantly abnormal. Different types of abnormalities can be observed, such as polymorphic delta activity, or epileptic spikes can display alterations and abnormalities. These abnormal EEG patterns allow to assess the severity of the coma and are related to prognosis. Based on previous work by Hockaday et al. [12], Synek et al. [13] suggested a scale classifying these patterns according to their prognosis. This scale has then been adapted by Young et al. in order to improve its reproducibility [6]. Young's scale is presented in Table 4.1 and gives information on the level of the coma. The higher the grade, the deeper the coma. Grade 1 corresponds to a slowing down of the EEG in comparison to a healthy subject. The slowing of the brain activity is proportional to the severity of the injury. The predominant rhythm is no longer the posterior alpha (8–12 Hz) present in healthy subjects but diffuse theta (4–7 Hz) or delta (1–3 Hz). If there is asymmetric brain damage, the EEG will likely also be asymmetric; the EEG above unaffected area can appear almost normal whereas that above affected area is severely impaired. Nevertheless, a precise location of a lesion cannot be achieved with the EEG as its spatial resolution is low [3].

Table 4.1 EEG classification of acute patients introduced by Young and collaborators [6]

Category	Subcategory
1. Delta/theta >50% of record (no theta coma)	(a) Reactivity
	(b) No reactivity
2. Triphasic waves	
3. Burst suppression	(a) With epileptiform activity
	(b) Without epileptiform activity
4. Alpha/theta/spindle coma (unreactive)	
5. Epileptiform activity (no burst-suppression pattern)	(a) Generalized
	(b) Focal or multifocal
6. Suppression	(a) <20 μV but >10 μV
	(b) <10 μV
Guidelines	
1. Burst-suppression pattern should present generalized flattening at standard sensitivity for more than 1 s at least every 20 s	
2. Suppression: for this category, voltage criteria should be met for the entire recording; there should be no reactivity	
3. When more than one category is present, select the most critical one	

It is important to test the reactivity of the EEG to eye opening/closing and external stimulations. A reactive EEG reflects a lighter coma and is associated with a better prognosis [3, 6, 14, 15]. Auditory or nociceptive stimulations can be used and should be performed 20–30s apart. A clear reactivity is a reproducible change in the background frequency and amplitude [15].

Higher grades are related to the apparition of specific patterns. Grade 2 corresponds to the occurrence of triphasic waves, that is, sharp deflections with two or three phases, the second phase having the highest amplitude. Grade 3 is related to burst-suppression pattern. Bursts of slow waves mingled with high frequency transients are followed by periods of flat EEG. In some cases of severe brain lesions, some comatose patients can display an EEG that is comparable to a normal wake EEG with a predominant alpha or theta rhythm but distributed differently to healthy subjects, as it is more frontally distributed—the alpha/theta coma (Grade 4). In the case of an alpha/theta coma, EEG does not react to stimulation according to most authors [6, 16] but not all [3, 17]. These patients must be differentiated from patients suffering a LIS or patients in a psychogenic coma. Indeed, in both the latter cases, the EEG can be close to normal [3]. The presence of epileptic activity despite antiepileptic medication corresponds to Grade 5.

The last stage of the coma is characterized by suppression (Grade 6), when there is no cerebral activity higher than 2 μV. An inactive EEG that lasts for more than 6 h in a patient who is not in hypothermia suggests prosencephalon death but not necessarily cerebral death as the EEG does not reflect the activity of the brainstem [5]. In some rare occasions, patients in "permanent vegetative state" can have an inactive EEG [3]. Similarly, drug intoxication can lead to an inactive EEG, but it is often reversible.

The interpretation of an EEG recording does not allow a prognostic statement if it is not combined with the etiology. Indeed, the characteristic features of the EEG are not specific to one etiology. Here are some examples of poor prognosis. In case of a cardiac arrest, a periodic generalized pattern is of poor prognosis. Following a hypoxia or metabolic encephalopathy, the apparition of suppression periods lasting several seconds that are not followed by a burst is of poor prognosis. A pattern such as alpha coma or alpha/theta coma is associated with different prognoses based on the etiology. For instance, if it is associated with a brainstem lesion, it is of poor prognosis. Importantly, to be of prognostic value, an EEG recording should not be done too early after the beginning of coma [13]. For a detailed review of prognosis associated with different patterns, we recommend the article by Brenner [3] or the chapter by Rossetti [15].

Evoked Potentials

Evoked potentials are components of the EEG obtained in response to particular events or sensory stimulation. They reflect the processing of the stimulus through time, from low-level peripheral receptive structures up to high-level associative

cerebral areas. The faster components, linked to the physical properties of the stimulus, are called *exogenous* and reflect the activation of neurons projecting toward the primary cortex. Belated components are linked to the psychological significance of the stimulus, the experimental conditions, and the level of awareness. They are called *endogenous* components and reflect the activity of subcortical and cortical structures, including associative areas. Evoked potentials allow an objective evaluation of patients' sensory, motor, and cognitive functions.

Somatosensory evoked potentials (SEPs) are obtained by transcutaneous electric stimulation of median nerves in the wrist. These potentials reflect the conduction of the nervous influx through the brachial plexus and its access to the primary somatosensory cortex [18]. A bilateral absence of the N20 in a comatose patient following circulatory arrest is highly associated with an absence of consciousness recovery (in 99–100% of cases) [19–22]. For other etiologies, the absence of SEP does not convey strong prognostic information. In traumatic brain injury, the absence of SEP could be due to a focal midbrain dysfunction or a focal cortical lesion [23] and is not a reliable predictor of poor prognosis [24]. In ischemic or hemorrhagic stroke, the absence of SEP correlates with poor outcome [25, 26]. In sepsis and septic shock, the patients often present delayed SEP peak latencies, but SEP does not help establishing a prognosis [24].

Brainstem auditory evoked potentials (BAEPs) are useful to study the conduction of the auditory signal via the auditory nerve and the protuberance. They appear within 10 ms. The absence of these potentials is associated with a poor recovery in patients with severe cerebral lesions but without peripheral auditory lesions [27, 28]. Nevertheless, this component has a lower predictive value than the N20 response [20]. Visual evoked potentials elicited by flashes are less common because they do not always trigger a response, even in healthy controls [29].

If the absence of exogenous components is often associated with a poor prognosis [30], the presence of exogenous components is not informative enough to be a marker of good prognosis. Clear exogenous components can be observed in patients that never recover.

More advanced cerebral processes, possibly reflecting the presence of consciousness, can be studied using cognitive evoked potentials. Until now they were exclusively studied with auditory tasks because comatose patients do not have eye-gaze control. They differ from exogenous evoked potentials in the sense that they are highly dependent on the experimental conditions. It is, thus, important to record these potentials when the patient is most vigilant and to ensure that the paradigm is optimized for recording the best potentials while minimizing the number of repetitions to avoid a habituation effect. Three components have been studied in acute patients: the N100 component in response to a stimulus, the mismatch negativity and the P3 in response to novelty, and the N400 and P600 components in response to semantic changes. Despite the fact that the presence of one of these components is related to good prognosis, they are less often recorded in acute patients. We believe that the main reasons for their limited use are the lack of clear guidelines to record these potentials, the influence of patient's fluctuations of vigilance on the components, the difficulty to assess the presence of a component, and the lack of

cohort studies relating these components to prognosis. The interpretation is especially problematic. Exogenous potentials are repeated hundreds to thousands of times with always the same "response." Endogenous potentials are repeated tens to hundreds of times with several factors influencing each repetition giving rise to slightly different "responses." To overcome these limitations, classic research average "response" over repetitions and over subjects leading to group average. This approach is not suitable for individual diagnosis or prognosis. To interpret the component waveform, researchers rely on several approaches balancing statistical test and a priori information on the location and latency of the component. Using too strict prior on location and latency may be problematic as brain damage may induce delayed latency and prevent the potential to be found above damaged areas. The statistical test should be strict enough to avoid false positive but flexible enough to detect weak component. Most groups use a different approach as no gold standard approach has been proposed yet.

The N100 component, a negative inflection that appears 100 ms after the start of the stimulus, indicates a response of the auditory cortex. This component is elicited by all types of stimuli and reveals that the auditory cortex is properly functioning. Its predictive value is, however, highly debated [31–34]. Aside from BAEPs, the N100 component would yet have a lower predictive value than the N20 response as regards consciousness recovery in comatose patients [20, 32, 33].

The mismatch negativity (MMN) is a negative component, which appears between 100 and 200 ms after a change or odd sound following a series of monotonous sounds. This component has low amplitude, which implies that a high number of repetitions are necessary for a good visualization. Since the MMN does not require the subject's attention, it indicates an automatic response triggered by the difference between the dissonant sound and the other preceding sounds which are still recorded in memory. Previous data obtained with an MMN paradigm in comatose patients suggest that this component beholds important predictive value independent of the etiology. Indeed, the presence of this response was related to very high probability of awakening [20, 31, 35–38].

The P3 is a positive inflection generated when the subject detects a rare and unexpected stimulus. For an auditory potential, it appears approximately 300 ms after the stimulus, while for a visual stimulus, it can appear 500 or 600 ms after the stimulus presentation. In case of cerebral lesions, its latency can be higher [39, 40]. The MMN and P3 are two different cerebral responses elicited by similar stimuli (deviant or novel), but they differ according to the time interval between stimuli. The MMN is generated when the stimuli are close to one another but disappears when the interval between two stimuli is longer than 2 s. The MMN originates from the superior temporal gyrus and from the frontal cortex. The P3 relates to the activation of a network of cerebral areas including frontoparietal regions [41]. The P3 is frequently linked to cognitive processes of higher complexity than the N100 and MMN components, such as categorization, decision-making, or updates in working memory. If simple sounds are sufficient for the generation of an MMN or a P3, the latter can also be generated by more complex stimuli. The emotional valence of these stimuli will have an impact on the amplitude. A stimulus such as the own

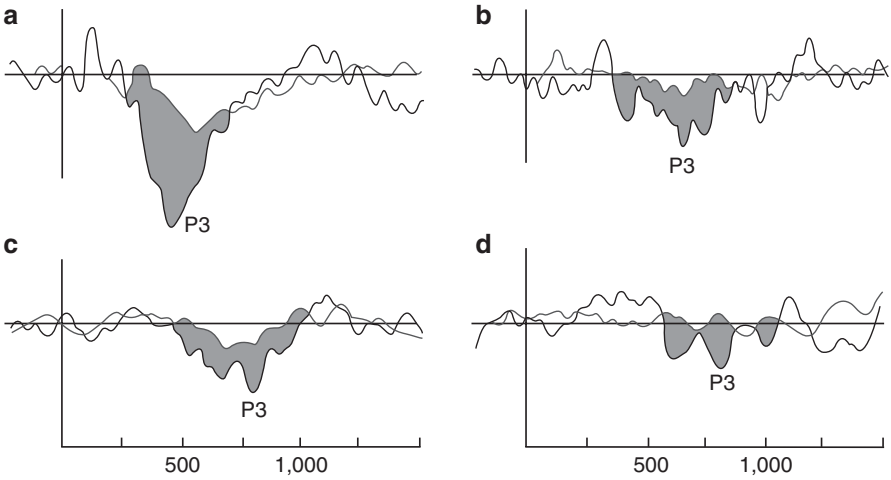

Fig. 4.1 Auditory evoked potentials in response to the own name in (**a**) healthy controls ($n = 5$) and (**b**) patients with a locked-in syndrome ($n = 4$), (**c**) with a minimally conscious state ($n = 6$), and (**d**) with an unresponsive wakefulness syndrome ($n = 5$). The area in *gray* represents the difference in activation between the presentation of the own name and the presentation of other names. A P3 response can be observed even in some patients in a vegetative state. Electrode Pz (Adapted from [30])

name will more likely trigger a P3 than a simple sound [42, 43] (Fig. 4.1). The presence of a P3 is related to good prognosis, but its absence does not convey any information [33, 44–46].

Quantitative EEG

Quantitative electroencephalography (QEEG) consists in the use of algorithms in order to extract complex measures likely to add objective information that can simplify the visual inspection of the EEG traces. For instance, one can compute the power spectral density of the signal at each electrode location to detect background rhythms, automatically detect epileptiform activities, or detect the presence of event-related potentials. Inherently, QEEG is less subjective than the visual analysis of the raw EEG signals and has been shown to offer better validity than visual scoring [47]. QEEG also facilitates the analysis of long-term EEG monitoring [48] or the repetition of recordings. Interestingly, the difference between two recordings in acute stage has been shown to be a good predictor of outcome in comatose patients [37, 49].

Automatic analysis of background EEG and reactivity has been proposed with methods based on burst-suppression ratio, entropy, or amplitude equivalent EEG or frequency decomposition and has shown to have prognostic implications [50–53].

The presence of event-related potential components has been investigated with machine learning [49, 54, 55]. Machine learning techniques are not biased by a priori hypotheses regarding electrode locations or latency of the components. Compared to the traditional techniques in this domain, they are also less affected by transient, artifact-contaminated activity recorded at certain electrodes. Furthermore, they provide a way to quantify differences in neural responses at the level of the single patient [49].

QEEG facilitates the analysis of long-term EEG monitoring [48] or the repetition of recordings. The difference between two recordings in acute stage has been shown to be a good predictor of outcome in comatose patients [37, 49].

Chronic Stage

EEG Visual Analysis

Recent studies have shown the interest of traditional EEG visual analysis for diagnosis in chronic severely brain-injured patients when describing EEG features according to standard clinical neurophysiological recommendations [56]. A recent work proposed a classification of the EEG of patients with DOC and compared it with behavioral testing and fMRI-based command-following [48]. They showed a significant correlation between the abnormality of the EEG and behavioral testing. Furthermore, all four patients showing fMRI evidence of command-following in the study also demonstrated well-organized EEG background during wakefulness and spindling activity during sleep, highlighting that EEG can be used as a complement to behavioral assessment for detecting the likelihood of unrecognized cognitive abilities in chronic DOC. Another study adapted the classification scheme (Table 4.2) and further demonstrated the usefulness of conventional EEG to disentangle patients in a chronic UWS from a MCS− and MCS+, with a better diagnostic reliability for traumatic patients than anoxic ones [57].

Table 4.2 EEG classification of chronic patients used by Estraneo and collaborators [57]

Category	Description
Normal activity	Predominant posterior alpha, anterior-posterior gradient, without focal or hemispheric slowing or epileptiform abnormalities
Mildly abnormal	Predominant posterior theta, symmetric or not, with frequent posterior alpha
Moderately abnormal	Predominant posterior theta, symmetric or not, with rare or occasional alpha, poorly organized anterior-posterior gradient
Diffuse slowing	Predominant diffuse theta or theta/delta, without anterior-posterior gradient
Low voltage	Predominant diffuse and low theta or delta (<20 μV)

Evoked Potentials

In acute patients, evoked potentials are used for their prognostic information. In chronic patients, researchers have studied their diagnostic power and concentrate their researches in finding the relationship between cognitive event-related potentials and patients' state of consciousness. Exogenous potentials are not very informative in chronic condition except that their absence prevents the interpretation of latter cognitive event [58].

At the group level, Kotchoubey et al. have shown that the MMN component could be present both in MCS patient (34%) and in UWS patients (65%) [59]. Interestingly, Wijnen et al. demonstrated that for ten UWS patients, the amplitude of the MMN was significantly higher in patients who evolved later to a MCS [60].

From a behavioral point of view, the distinction between these two states can be made based on response to command. Hence, active evoked potentials are used to better evaluate consciousness in a patient as it requires his/her active participation, which differs from passive listening. In a study, patients were asked to count occurrences of their own name, presented along with seven other names; some MCS patients displayed a P3 of greater amplitude than when passively listening to their name. On the other hand, UWS patients who showed a P3 in response to their name did not display higher amplitudes when asked to actively count their names [43]. This paradigm confirmed the presence of conscious processing in a LIS patient [61]. However, one study reported increased P3 amplitude in behaviorally unresponsive patients during active task based on a deviant tone [62]. An extensive research on attention involving healthy subjects has suggested that the P3 response should be decomposed into separable subcomponents called the P3a and P3b. The relatively early, frontally located P3a is thought to reflect exogenous attention, triggered by "bottom-up" stimulus novelty that may be task irrelevant. The later, parietally centered P3b, on the other hand, is suggested to be a marker of "top-down" or volitional engagement of endogenous attention to task-relevant targets to be consolidated into working memory and made available for conscious access. Chennu et al. [63] developed a task designed to engender such exogenous or endogenous attention, as indexed by the P3a and P3b components, using pairs of word stimuli presented auditorily among distractors. Results suggested that bottom-up and top-down attentional processing might be preserved in some patients in a MCS and UWS. However, the level of difficulty required by this task seems to be too high to enable a good rate of detection of conscious patients.

In the same idea, another study used a different auditory P3-based paradigm based on tone stream segregation allowing for binary decisions [64] in a small cohort of chronic DOC patients. Two tone streams with infrequently and randomly appearing deviant tones were presented to the patient. The patient was asked to count the number of deviants in one stream, in order to modulate the P3 response to the attended stream. Only five patients could achieve results above chance level, and none of them achieved performances allowing communication with the system.

Another auditory paradigm assessed the participant's ability to pay attention to global violations of temporal regularities, the local-global paradigm [65–67]. This paradigm involves sequences of auditory stimuli of either identical tones, called locally standard, or identical tones and a deviant tone, called locally deviant. Here, the term "local" refers to a single sequence. The locally deviant sequences typically lead to a MMN. Alternatively, the term "global" refers to irregularities between sequences. For example, if 80% of sequences are locally deviant, these are the ones considered globally standard, while the remaining 20%, which are locally standard, will be the globally deviant sequences since these are the minority. Global deviant sequences generate a late P3b response. When tested on patients, this paradigm had 34% sensitivity of detecting the ability to follow a command and 88% specificity.

Another candidate biomarker of consciousness is the N400, a negative inflection which appears roughly 400 ms after a word presentation. Its amplitude is increased if the stimulus is discordant (semantic or phonologic discordances) based on the context (word or sentence). Care must be taken, however, as a semantic incongruence can also lead to a P600, a positive inflection which appears 600 ms after stimulus presentation. Any change, negative or positive, can, thus, be considered as incongruence processing. These inflections have been found in MCS and UWS patients preventing their interpretation as a diagnosis marker [68, 69]. However, their presence has been suggested as a marker of good prognosis in less than a year patients [69].

Evoked potentials are complementary to behavioral studies in patients. It was first suggested to present them in a hierarchical approach [70] where low-level functionalities are first evaluated with exogenous potentials and then higher-level processing is tested with cognitive potentials. The latter is presented in passive and then in active tasks. However, recent researches tend to show that patients may present a response to an active paradigm while no activation was detected with a passive paradigm. Active paradigms may therefore convey more information than the passive ones. If the patient answers to the active task, this is suggested to be equivalent to a behavioral response to command. At this stage, it becomes important to test communication tools with the patient such as brain-computer interfaces (see below).

Background Rhythms, Connectivity, and Complexity

The quantitative EEG analysis has shown a slowing down of the EEG in patients with DOC in comparison to healthy participants, more marked in UWS than in MCS patients [71, 72]. UWS and MCS patients showed an increase of delta power and a decreased alpha power. Such findings can also be observed through visual analysis of the EEG traces (Fig. 4.2) [71, 73].

The EEG can also help to quantify the functional connectivity between cerebral areas [74]. PET and fMRI studies have reported a disrupted functional connectivity in patients suffering from disorders of consciousness [75–78]. Computing the coupling between electrodes provides a connectivity measure of underlying brain areas.

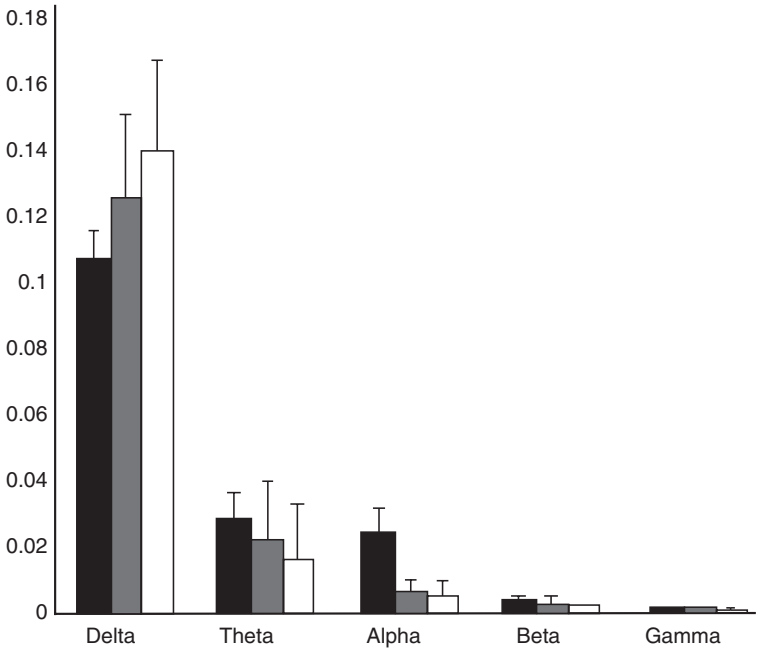

Fig. 4.2 Normalized power spectral density computed at Cz in five different frequency bands in healthy controls (*black*; $n = 5$), patients in a minimally conscious state (*gray*; $n = 12$, MCS), and patients in an unresponsive wakefulness syndrome (*white*; $n = 10$, UWS). Patients with disorders of consciousness have more power in low-frequency bands and less power in higher-frequency bands, suggesting a slowing down EEG activity

This measure gives complementary information that can be used for diagnostic and prognostic purposes. A study on a single patient with UWS with right hemisphere lesion showed a diminution of the functional connectivity in the damaged hemisphere. Such decrease was not visible using spectral power measures [79]. Group studies confirmed the decreased connectivity in patients with UWS and showed a slighter decreased functional connectivity in patients with MCS [71, 80–82].

Tools based on the complexity of the signal and initially developed for anesthesia monitoring have been proposed to evaluate the level of consciousness in severely brain-injured patients. These tools are used in the clinical field to measure the depth of anesthesia and to prevent the patient's arousal during a surgical procedure, while allowing drug savings and a faster postoperative awakening, thanks to a better control of the depth of anesthesia. Furthermore, they are easy to use and interpret. For example, the bispectral index (BIS) is a unitless measure ranging from 0 (inactive EEG) to 100 (normal activity), which results from a combination of temporal and frequency parameters [83]. BIS values correlate with the decrease of vigilance observed during the different sleep stages [84]. In case of disorders of consciousness, UWS patients have a lower BIS value than patients in a MCS, but this value cannot systematically differentiate patients in a UWS from patients in a MCS at an individual level [85]. Similar results were obtained using the EEG spectral entropy [86, 87].

These results were obtained at group level. Individual BIS or entropy values are not accurate enough to establish a diagnosis in chronic stage.

The potential of EEG frequency power, functional connectivity, and complexity are also highlighted by the results of machine learning studies. They are reliable measures to differentiate between UWS, MCS, and conscious participants according to a cohort study involving 113 patients [54]. Functional connectivity is the best measure distinguishing MCS from UWS in another cohort of 54 patients [88].

Long-Term EEG: Polysomnography

Sleep is characterized by behavioral decreases in vigilance as characterized by the presence of eye closure and muscle inactivity, as well as a number of electrophysiological features such as slow waves, spindles, and rapid eye movement and non-rapid eye movement [89]. These sleep patterns may be an adaptive phenomenon to maintain global brain integrity as they have been shown to be altered in pathologies such as stroke [90] and Alzheimer's disease [91]. A better understanding of sleep cycles and architecture of patients with DOC might therefore provide useful information about diagnosis and prognosis in this population [92].

In 2011, Landsness et al. studied sleep pattern using EEG high density in 11 patients with DOC [93]. They reported that clear EEG changes could be observed by visual analysis in all MCS patients during decreases in behavioral vigilance. In addition, the majority of these patients had several EEG features typical of normal sleep (i.e., all patients showed an alternating non-rapid eye movement/rapid eye movement sleep pattern and a homoeostatic decline of EEG slow-wave activity through the night). On the other hand, even though preserved behavioral sleep was observed in all UWS patients, no clear changes were observed during periods of eye closure as compared with periods with eyes opened. In particular, no slow-wave sleep or rapid eye movement sleep stages were identified, and no homoeostatic regulation of sleep-related slow-wave activity was observed. This study supports the relationship between sleep electrophysiology and the level of consciousness in patients with DOC, and sleep study could help improve the diagnosis of these patients.

These findings were then supported by other studies performed elsewhere also reporting the importance of preserved sleep patterns for consciousness [48, 94], some of them also reporting the potential prognostic value of the presence of specific features (i.e., sleep spindles) for further recovery of consciousness [95, 96].

Electromyography

Bekinschtein et al. studied DOC patients using electromyography (EMG, recording of muscle activity) [97] to detect signs of command-following unobservable with the naked eye. They presented four different 30s—blocks of commands to the

patient, “Please try to move your right hand” and “Please try to move your left hand,” and two control phrases, “Today is a sunny day” and “It is raining outside today.” At the end of the block, the instruction was “Please do not move, stay still.” They observed an increased EMG signal specifically linked to command in several cases of patients in a MCS or UWS, suggesting that EMG could be used to objectively detect subthreshold motor response in this population.

Following this work, Habbal and colleagues [98] used a similar method to investigate the impact of the type of movements used (i.e., “Move your hands,” “Move your legs,” and “Clench your teeth”), on a bigger cohort of patients. Supporting previous results, they reported willful EMG responses in a small group of patients. In addition, they observed a better response with the stimulus “Move your hands” in both healthy controls and patients, confirming that EMG could help to detect voluntary movements in this population. Finally, Lesenfants and colleagues [99] proposed a new methodology based on single-trial analysis for detecting residual response to command with EMG in patients with DOC. The use of single-trial evaluation of response to command allows to overcome the issue of trial dependency and decrease the influence of a patient’s fluctuation of vigilance or arousal over time on diagnostic accuracy. They illustrated a response to command in all MCS cases displaying reproducible response to command at bedside on multiple assessments, even though only 6 of the 14 individuals presented a behavioral response to command on the day of the EMG assessment.

Brain-Computer Interface

A brain-computer interface (BCI) is a system allowing for communication between the brain and the external environment. It is independent from any peripheral neural or muscular activity, and it directly converts brain activity into a computerized command [100]. BCIs could be of interest particularly for communicating with patients whose cognitive functions are intact but are paralyzed and anarthric following a neurological or muscular damage, e.g., patients with a LIS [101]. These patients will present a normal EEG or a response to an active paradigm. Simple augmentative and alternative communication tools have been developed to allow communication with these patients. The simplest are based on the tracking of residual motor function such as head or eye movements [102]. Character’s selection is made with dwell, physical click, or blink. For people with severe motor disabilities, a simple yes-no communication can be achieved [e.g., one eye blink for yes, two blinks for no]. However, these methods are based on the patient’s residual motor ability. In some cases, it is necessary to use a communication system that does not involve motor skills at all. Those motor-independent systems are not only useful for using alphabetic systems and expressing more complex ideas [103]. BCIs could be the key to providing access to the outside world for a LIS patient [104]. Finally, beyond

communication, BCIs have also inspired new approaches to detect a response to a command in the absence of discernible behavior at the bedside [105].

A BCI is based on cerebral activity measured using techniques, such as electroencephalography (EEG), functional magnetic resonance imagery (fMRI), implanted electrodes (intracortical recording or electrocorticography), or functional near-infrared spectroscopy (fNIRS) in order to control the environment [106]. A BCI is not a "mind-reading" device. Its primary function is to decode brain activity and map it with a set of continuous or discrete selections to allow a subject to choose between different options. This choice is made through the control of neuroelectrical activity in real time [107–109]. A specific algorithm translates the extracted features into commands that represent the user's intent. These commands can control effectors to select items (e.g., words). Recent development has shown the usefulness of BCIs in controlling motor prosthesis, cursors, access to internet, and communication [109–114]. Here, we will focus on systems allowing functional communication with the surrounding and will present the recent progress in the development of BCIs. Moreover, we discuss clinical applications in LIS patients and studies performed in patients recovering from coma.

EEG-Based BCI

EEG-based BCI paradigms have been developed through testing with healthy controls and severely motor disabled (LIS, e.g., amyotrophic lateral sclerosis (ALS) [109, 115]) and more recently with patients with DOC. EEG-based BCIs use ERPs, more precisely components such as the P3 or steady-state visually evoked potentials (SSVEPs), sensorimotor rhythms (SMRs), slow cortical potentials (SCPs), and the alpha rhythm. Studies usually report a great heterogeneity in the results depending on the population, the method (from the cognitive task to data analyses), and the modality involved.

The most widely used ERP component is the P3. Donchin and his colleagues have developed a visual BCI using a 6 × 6 matrix composed of letters and signs [116]. The rows and columns are successively illuminated. The participant has to focus his/her attention on the letter he/she wants to spell, eliciting a P3. With this type of BCI, users would be able to spell up to 7–8 letters per minute with an accuracy of 80–90%. One study showed that it was possible to establish communication [115] in five out of six ALS patients using this visual P3-based paradigm developed by Donchin [116]. Four of them could use the system later for spelling words and demonstrated functional communication. As visually based BCIs could be hard to implement in patients with gaze control impairment, Kübler has adapted the use of a matrix in the auditory modality. Five rows and five columns represented the letters of the alphabet [117]. The five lines were associated with a number between 1 and 5 and the five columns with a number between 6 and 10. The numbers were

auditorily presented and the patient selected the row and the column of the target letter. Four ALS patients were evaluated with this system, demonstrating adequate performance for visual (more than 70%) but not for auditory (just above chance level) communication. Moreover, users reported more difficulty to concentrate during the auditory condition.

Lugo and colleagues investigated the use of a vibrotactile paradigm to trigger P3 responses in patients with LIS for establishing somatosensory BCI-based communication. They were asked to first count a target stimulus and then answer five questions by counting the vibrations on either the right wrist for "yes" or the left wrist for "no." Four patients achieved 100% accuracy during the counting task, whereas one patient achieved 100% accuracy during the communication. These findings support the feasibility of eliciting a P3 response using vibrotactile stimulation in patients with LIS. This approach is currently tested for the detection of consciousness in DOC, but no results have been published at this moment.

To our knowledge, Lulé et al. performed the first study in patients with DOC [118]. They used the Sellers and Donchin's P3 paradigm using auditory stimuli (yes, no, stop, go) [107] to test its reliability as a diagnostic tool for DOC. If the study showed the feasibility of applying a BCI system in chronic patients with DOC, only one MCS and one LIS patient achieved offline performance above chance level suggesting a response to command (Fig. 4.3). These results suggest that the BCI system cannot ensure the absence of consciousness in case of negative results [118], especially as the use of such paradigms may be limited by the patient's sensory impairment (e.g., auditory, visual).

Finally, Chatelle et al. [119] investigated the applicability of a visual P3-based and an SSVEP-BCI to communicate with patients with incomplete LIS by looking at BCI performance, mental workload, and overall satisfaction with both systems. If all of the seven patients included were able to achieve an accuracy of 70% or higher with the SSVEP-based BCI, only three patients could achieve that with the P3-based BCI. In addition, the SSVEP-based BCI was associated with a lower mental workload and a higher overall satisfaction, suggesting that the SSVEP might be more suitable for patients with severe motor disabilities. On the other hand, such SSVEP paradigms are highly dependent on eye movements, which can be very limited in patients with DOC. To overcome this issue, Lesenfants et al. [120] developed a gaze-independent SSVEP-BCI based on covert attention. Two out of the six LIS patients included could reach accuracy above chance level offline, illustrating a response to a command, whereas one patient could communicate online, suggesting that covert SSVEP is feasible but there is a clear need for further improvement in order to provide more sensitive tools that could be used for diagnosis and/or communication in severely brain-injured patients.

Changes in SMRs or μ rhythms have also been used for BCI purposes. SMRs refer to EEG activity of 8–15 Hz that can be recorded in primary sensorimotor areas [100] and which is usually accompanied by a beta activity (18–26 Hz). This activity can be reduced or desynchronized by preparing, executing, or imagining a movement (event-related desynchronization), particularly in the contralateral motor

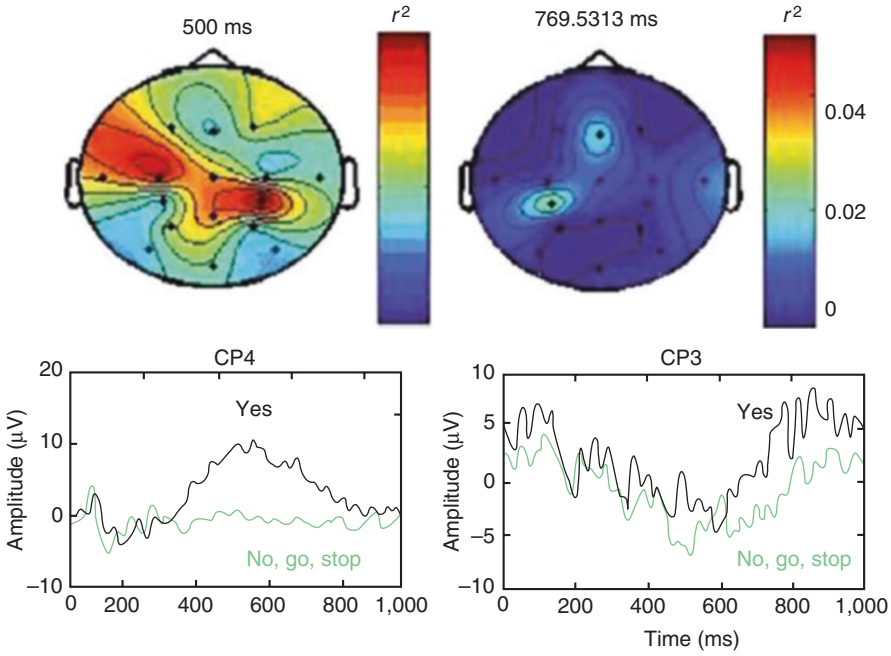

Fig. 4.3 P3 in a healthy volunteer (*left*) and a patient in a minimally conscious state (*right*) in response to the target stimulus *yes*. On the *top*, distribution of the observed response to target stimuli can be seen (yes). The *colors* in the images *in the upper row* represent the difference in the observed response between the target stimuli and nontarget stimuli. The greater the difference, the more the region is colored *red-orange*. Below, averaging overall responses for the other three stimuli (nontargets no, stop, go; in *green*) and for all responses to target stimuli (yes; in *brown*) is shown (Adapted from [118])

region. An increase in the SMR, or synchronization, occurs following the execution of a movement and during relaxation [121]. The advantage here is that these components do not require the actual execution of the movement but solely the kinesthetic mental imagery of this [122]. However, it is not possible to use more than two commands, the increase to three or more leading to a decrease in the classification accuracy. In healthy subjects, many BCIs have shown satisfying results in producing words based on visual [25] and auditory [26] input. The lowest frequencies of signals generated by the cortex and recorded at the scalp are the SCPs. The negative SCPs are usually associated with movements and other functions that involve cortical activation, while positive SCPs are usually associated with a reduction in cortical activity [27]. This system is also limited to two (or less) commands. It has been shown that it is possible to teach participants to control their brain activity (i.e., the SCPs) to move an object on a screen [28]. Using SMRs, Neuper and colleagues [123] have trained a paralyzed patient to use a language support program (LSP, [124]) in order to communicate. The spelling involved the selection of a letter in

successive steps using a virtual keyboard. A predefined set of letters was divided into two subsets and presented at the top and at the bottom of the screen. The patient was instructed to select one of this subset by either relaxing or by using motor imagery. When the patient had selected the subset containing the target letter, this subset was itself divided into two parts, and this until the patient selected the target letter. After several months, the patient was able to control the keyboard with an accuracy of 70%. Another study showed the possibility for a patient with ALS to use a keyboard by the control of SMRs [125].

SMRs have been well studied for BCI and have inspired some approaches for patients with DOC. Goldfine and colleagues [126] recorded EEG from three patients showing command-following at the bedside, while they were asked to perform in motor imagery and spatial navigation imagery. If all patients demonstrated the capacity to generate mental imagery on the same tasks on independent fMRI studies, two of them also showed evidence of modulation of EEG activity during the imagery tasks.

In a further study from Cruse et al., motor imagery tasks were investigated in a cohort of 16 UWS [127] and then in 23 MCS patients [128]. Findings suggested that about 20% were able to voluntary control their brain activity in response to a command ("imagine squeezing your right hand" versus "imagine moving all your toes"). The methodology used in this latter study raised the challenge of assessing patient with DOC. Indeed, in this study, blocks of trials (15 beeps following an instruction) were used in order to decrease the cognitive load associated with the tasks. However, if the use of blocks is usually not an issue in healthy volunteers who present relatively stable EEG over time, it can be a problem in noncommunicative or noncollaborative patients showing nonstationarities in the signal (e.g., vigilance fluctuation or important motor artifacts). Indeed, those patients are more likely to present changes in the EEG which could influence trials and blocks dependencies, leading to a misestimation of the results. This emphasizes the need for appropriate statistical tests and paradigms for that kind of BCI application in severely brain-injured population, as well as the necessity for reanalysis of data using different methods [129, 130]. The paradigm was then improved to decrease the working memory load and circumvent the block design issue. In this paradigm, each trial is started with one of the three instructions (i.e., "Try to move your right hand," "Try to move your left hand," and "And now, relax") that are presented auditorily in a randomized order. The utility of the method as a diagnostic tool has been reported in a single patient diagnosed as being clinically diagnosed in an UWS [131].

Finally, using a combination of different EEG responses for assessing DOC has been recently suggested by Pan and colleagues [132]. In this study, the subject's own face and an unfamiliar face were randomly displayed on the left and right side of a computer screen. The left and right images were flickering at different frequencies, whereas the two image frames also flashed in a random order, eliciting both SSVEP and P3 responses. The LIS patient and 28% of the patient with DOC were able to selectively attend to their own or the unfamiliar image, supporting the idea that hybrid BCI systems could be used as a supplemental bedside tool to detect awareness in patients with DOC.

Invasive BCI

So far, we have presented BCIs using noninvasive systems. As many systems are based on EEG signals measured on the scalp, the quality of recordings is relatively low (distorted signal and low amplitude), the spatial resolution is limited, and training is necessary. Therefore, some studies have focused on invasive recording methods. Recordings are performed either directly at the neuronal level [133–136] or on the brain surface in the case of an electrocorticographic recording [137–139]. BCIs based on intracortical microelectrodes can directly record the activity of neurons and provide a stronger signal. These allow users to control devices such as computer cursors more quickly and accurately [139]. While this technique has not been tested in healthy subjects, participants with ALS showed good performances in the context of complex communication with continuous point-and-click control [140].

Conclusion and Perspectives

The role and potential utility of the EEG have greatly evolved in the last years. The interpretation of the EEG trace is not anymore limited to acute patients and for the monitoring of epileptic activity. Long-term EEG or repeated evaluations are recommended and have shown their importance for diagnostic and prognostic estimation (e.g., EEG reactivity and the presence of sleep patterns). If visual analysis was suggested to provide sufficient information, it can be very time-consuming for clinicians. The development of automated EEG analysis tools should make it more feasible in clinical setting.

The exogenous evoked potentials can also give useful information as regards the patient's prognosis (e.g., N20) and remnant stimulus processing. Their absence is often associated with a bad prognosis. Active cognitive evoked potentials have the potential to improve the detection of signs of consciousness such as response to command in behaviorally unresponsive patients. The active protocols should, however, be standardized and tested on extensive cohort. Besides evoked potentials, active protocols, inspired by BCI research, have been developed based on several sensory modalities. These could be used to improve the clinical diagnosis as it has already been suggested by fMRI and EEG studies. However, the typical vigilance fluctuation observed in DOC patients is a major confounding factor for these applications [141]. Many patients have been evaluated, and only a few have shown signs of consciousness with these paradigms, including patients showing signs of consciousness at the bedside. Further research is needed to clarify whether this is due to a lack of awareness in some patients, the cognitive load associated with the paradigms, the presence of vigilance fluctuation [142], sensory impairments, or the analysis method used. In the future, it is also important to develop systems that are reliable and easy to use in the everyday life. New algorithms should include the automatic detection of artifacts, the single-trial classification, and the possibility to classify a session without training sessions.

In conclusion, EEG represents a very useful tool for the assessment of acute and chronic DOC patients. The information gathered with the EEG should be combined with behavioral and neuroimaging evaluations to improve the prognosis and diagnosis of the patients.

References

1. Guideline seven: a proposal for standard montages to be used in clinical EEG. American Electroencephalographic Society. J Clin Neurophysiol. 1994;11(1):30–6.
2. Krauss GL, Fisher RS. The Johns Hopkins atlas of digital EEG: an interactive training guide. Baltimore: The Johns Hopkins University Press; 2006.
3. Brenner RP. The interpretation of the EEG in stupor and coma. Neurologist. 2005;11(5): 271–84.
4. Young GB. The EEG in coma. J Clin Neurophysiol. 2000;17(5):473–85.
5. Posner JB, et al. The diagnosis of stupor and coma. 4th ed. New York: Oxford University Press; 2007.
6. Young GB, et al. An electroencephalographic classification for coma. Can J Neurol Sci. 1997;24(4):320–5.
7. Alvarez V, Rossetti AO. Clinical use of EEG in the ICU: technical setting. J Clin Neurophysiol. 2015;32(6):481–5.
8. Privitera M, et al. EEG detection of nontonic-clonic status epilepticus in patients with altered consciousness. Epilepsy Res. 1994;18(2):155–66.
9. Claassen J, et al. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. Neurology. 2004;62(10):1743–8.
10. Woo Lee J. Which EEG patterns deserve treatment in the ICU? In: Rossetti A, Laureys S, editors. Clinical neurophysiology in disorders of consciousness: brain function monitoring in the ICU and beyond. Wien: Springer; 2015.
11. Kaplan PW. The clinical features, diagnosis, and prognosis of nonconvulsive status epilepticus. Neurologist. 2005;11(6):348–61.
12. Hockaday JM, et al. Electroencephalographic changes in acute cerebral anoxia from cardiac or respiratory arrest. Electroencephalogr Clin Neurophysiol. 1965;18:575–86.
13. Synek VM. Prognostically important EEG coma patterns in diffuse anoxic and traumatic encephalopathies in adults. J Clin Neurophysiol. 1988;5(2):161–74.
14. Rossetti AO, et al. Prognostication after cardiac arrest and hypothermia: a prospective study. Ann Neurol. 2010;67(3):301–7.
15. Rossetti AO. Prognostic utility of electroencephalogram in acute consciousness impairment. In: Rossetti AO, Laureys S, editors. Clinical neurophysiology in disorders of consciousness. New York: Springer; 2015.
16. Berkhoff M, Donati F, Bassetti C. Postanoxic alpha (theta) coma: a reappraisal of its prognostic significance. Clin Neurophysiol. 2000;111(2):297–304.
17. Westmoreland BF, et al. Alpha-coma. Electroencephalographic, clinical, pathologic, and etiologic correlations. Arch Neurol. 1975;32(11):713–8.
18. Guerit JM. Evoked potentials in severe brain injury. Prog Brain Res. 2005;150:415–26.
19. Amantini A, et al. Prediction of 'awakening' and outcome in prolonged acute coma from severe traumatic brain injury: evidence for validity of short latency SEPs. Clin Neurophysiol. 2005;116(1):229–35.
20. Fischer C, et al. Improved prediction of awakening or nonawakening from severe anoxic coma using tree-based classification analysis. Crit Care Med. 2006;34(5):1520–4.

21. Lew HL, et al. Use of somatosensory-evoked potentials and cognitive event-related potentials in predicting outcomes of patients with severe traumatic brain injury. Am J Phys Med Rehabil. 2003;82(1):53–61. quiz 62–4, 80
22. Robinson LR, et al. Predictive value of somatosensory evoked potentials for awakening from coma. Crit Care Med. 2003;31(3):960–7.
23. Cruccu G, et al. Recommendations for the clinical use of somatosensory-evoked potentials. Clin Neurophysiol. 2008;119(8):1705–19.
24. Tjepkema-Cloostermans M, van Putten M, Horn J. Prognostic use of somatosensory evoked potentials in acute consciousness impairment. In: Rossetti A, Laureys S, editors. Clinical neurophysiology in disorders of consciousness. Wien: Srpinger; 2015.
25. Su YY, et al. Parameters and grading of evoked potentials: prediction of unfavorable outcome in patients with severe stroke. J Clin Neurophysiol. 2010;27(1):25–9.
26. Zhang Y, et al. Predicting comatose patients with acute stroke outcome using middle-latency somatosensory evoked potentials. Clin Neurophysiol. 2011;122(8):1645–9.
27. de Sousa LC, et al. Auditory brainstem response: prognostic value in patients with a score of 3 on the Glasgow Coma Scale. Otol Neurotol. 2007;28(3):426–8.
28. Haupt WF, Pawlik G, Thiel A. Initial and serial evoked potentials in cerebrovascular critical care patients. J Clin Neurophysiol. 2006;23(5):389–94.
29. Vanhaudenhuyse A, Laureys S, Perrin F. Cognitive event-related potentials in comatose and post-comatose states. Neurocrit Care. 2008;8(2):262–70.
30. Laureys S, et al. Residual cognitive function in comatose, vegetative and minimally conscious states. Curr Opin Neurol. 2005;18:726–33.
31. Fischer C, et al. Predictive value of sensory and cognitive evoked potentials for awakening from coma. Neurology. 2004;63(4):669–73.
32. Glass I, Sazbon L, Groswasser Z. Mapping "cognitive" event-related potentials in prolonged postcoma unawareness state. Clin Electroencephalogr. 1998;29(1):19–30.
33. Guerit JM, et al. ERPs obtained with the auditory oddball paradigm in coma and altered states of consciousness: clinical relationships, prognostic value, and origin of components. Clin Neurophysiol. 1999;110(7):1260–9.
34. Mutschler V, et al. Auditory P300 in subjects in a post-anoxic coma. Preliminary data. Neurophysiol Clin. 1996;26(3):158–63.
35. Kane NM, et al. Event-related potentials--neurophysiological tools for predicting emergence and early outcome from traumatic coma. Intensive Care Med. 1996;22(1):39–46.
36. Naccache L, et al. Auditory mismatch negativity is a good predictor of awakening in comatose patients: a fast and reliable procedure. Clin Neurophysiol. 2005;116(4):988–9.
37. Tzovara A, et al. Prediction of awakening from hypothermic post anoxic coma based on auditory discrimination. Ann Neurol. 2016; doi:10.1002/ana.24622.
38. Rossetti AO, et al. Automated auditory mismatch negativity paradigm improves coma prognostic accuracy after cardiac arrest and therapeutic hypothermia. J Clin Neurophysiol. 2014;31(4):356–61.
39. Munte TF, Heinze HJ. Brain potentials reveal deficits of language processing after closed head injury. Arch Neurol. 1994;51(5):482–93.
40. Granovsky Y, et al. P300 and stress in mild head injury patients. Electroencephalogr Clin Neurophysiol. 1998;108(6):554–9.
41. Pegado F, et al. Probing the lifetimes of auditory novelty detection processes. Neuropsychologia. 2010;48(10):3145–54.
42. Perrin F, et al. Brain response to one's own name in vegetative state, minimally conscious state, and locked-in syndrome. Arch Neurol. 2006;63:562–9.
43. Schnakers C, et al. Voluntary brain processing in disorders of consciousness. Neurology. 2008;71:1614–20.
44. Yingling CD, Hosobuchi Y, Harrington M. P300 as a predictor of recovery from coma. Lancet. 1990;336(8719):873.

45. Gott PS, Rabinowicz AL, DeGiorgio CM. P300 auditory event-related potentials in nontraumatic coma. Association with Glasgow Coma Score and awakening. Arch Neurol. 1991; 48(12):1267–70.
46. Fischer C, Dailler F, Morlet D. Novelty P3 elicited by the subject's own name in comatose patients. Clin Neurophysiol. 2008;119(10):2224–30.
47. Thatcher RW. Validity and reliability of quantitative electroencephalography. J Neurother. 2010;14(2):122–52.
48. Forgacs PB, et al. Preservation of electroencephalographic organization in patients with impaired consciousness and imaging-based evidence of command-following. Ann Neurol. 2014;76(6):869–79.
49. Tzovara A, et al. Progression of auditory discrimination based on neural decoding predicts awakening from coma. Brain. 2013;136(Pt 1):81–9.
50. Wennervirta JE, et al. Hypothermia-treated cardiac arrest patients with good neurological outcome differ early in quantitative variables of EEG suppression and epileptiform activity. Crit Care Med. 2009;37(8):2427–35.
51. Rundgren M, Rosen I, Friberg H. Amplitude-integrated EEG (aEEG) predicts outcome after cardiac arrest and induced hypothermia. Intensive Care Med. 2006;32(6):836–42.
52. Rundgren M, et al. Continuous amplitude-integrated electroencephalogram predicts outcome in hypothermia-treated cardiac arrest patients. Crit Care Med. 2010;38(9):1838–44.
53. Noirhomme Q, et al. Automated analysis of background EEG and reactivity during therapeutic hypothermia in comatose patients after cardiac arrest. Clin EEG Neurosci. 2014;45(1): 6–13.
54. Sitt JD, et al. Large scale screening of neural signatures of consciousness in patients in a vegetative or minimally conscious state. Brain. 2014;137(Pt 8):2258–70.
55. King JR, et al. Single-trial decoding of auditory novelty responses facilitates the detection of residual consciousness. Neuroimage. 2013;83C:726–38.
56. American Clinical Neurophysiology Society. Guideline 7: guidelines for writing EEG reports. J Clin Neurophysiol. 2006;23(2):118–21.
57. Estraneo A, et al. Standard EEG in diagnostic process of prolonged disorders of consciousness. Clin Neurophysiol. 2016;127(6):2379–85.
58. Kotchoubey B. First love does not die: a sustaining primacy effect on ERP components in an oddball paradigm. Brain Res. 2014;1556:38–45.
59. Kotchoubey B, et al. Information processing in severe disorders of consciousness: vegetative state and minimally conscious state. Clin Neurophysiol. 2005;116(10):2441–53.
60. Wijnen VJ, et al. Mismatch negativity predicts recovery from the vegetative state. Clin Neurophysiol. 2007;118(3):597–605.
61. Schnakers C, et al. Detecting consciousness in a total locked-in syndrome: an active event-related paradigm. Neurocase. 2009;4:1–7.
62. Real RG, et al. Information processing in patients in vegetative and minimally conscious states. Clin Neurophysiol. 2016;127(2):1395–402.
63. Chennu S, et al. Dissociable endogenous and exogenous attention in disorders of consciousness. Neuroimage Clin. 2013;3:450–61.
64. Pokorny C, et al. The auditory P300-based single-switch brain-computer interface: paradigm transition from healthy subjects to minimally conscious patients. Artif Intell Med. 2013; 59(2):81–90.
65. Faugeras F, et al. Probing consciousness with event-related potentials in the vegetative state. Neurology. 2011;77(3):264–8.
66. King JR, et al. Information sharing in the brain indexes consciousness in noncommunicative patients. Curr Biol. 2013;23(19):1914–9.
67. Bekinschtein TA, et al. Neural signature of the conscious processing of auditory regularities. Proc Natl Acad Sci U S A. 2009;106(5):1672–7.
68. Kotchoubey B. Event-related potential measures of consciousness: two equations with three unknowns. Prog Brain Res. 2005;150:427–44.

69. Steppacher I, et al. N400 predicts recovery from disorders of consciousness. Ann Neurol. 2013;73(5):594–602.
70. Kubler A, Kotchoubey B. Brain-computer interfaces in the continuum of consciousness. Curr Opin Neurol. 2007;20(6):643–9.
71. Lehembre R, et al. Resting-state EEG study of comatose patients: a connectivity and frequency analysis to find differences between vegetative and minimally conscious states. Funct Neurol. 2012;27(1):41–7.
72. Lechinger J, et al. CRS-R score in disorders of consciousness is strongly related to spectral EEG at rest. J Neurol. 2013;260(9):2348–56.
73. Leon-Carrion J, et al. Brain function in the minimally conscious state: a quantitative neurophysiological study. Clin Neurophysiol. 2008;119(7):1506–14.
74. Pereda E, Quiroga RQ, Bhattacharya J. Nonlinear multivariate analysis of neurophysiological signals. Prog Neurobiol. 2005;77(1–2):1–37.
75. Laureys S. The neural correlate of (un)awareness: lessons from the vegetative state. Trends Cogn Sci. 2005;9:556–9.
76. Laureys S, et al. Impaired effective cortical connectivity in vegetative state: preliminary investigation using PET. Neuroimage. 1999;9(4):377–82.
77. Vanhaudenhuyse A, et al. Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. Brain. 2010;133(Pt 1):161–71.
78. Soddu A, et al. Identifying the default-mode component in spatial IC analyses of patients with disorders of consciousness. Hum Brain Mapp. 2012;33(4):778–96.
79. Davey MP, Victor JD, Schiff ND. Power spectra and coherence in the EEG of a vegetative patient with severe asymmetric brain damage. Clin Neurophysiol. 2000;111(11):1949–54.
80. Schiff N Large scale brain dynamics and connectivity in the minimally conscious state. In Handbook of brain connectivity. New York: Springer; 2007. p. 505–20.
81. Pollonini L, et al. Information communication networks in severe traumatic brain injury. Brain Topogr. 2010;23(2):221–6.
82. Fingelkurts AA, et al. EEG oscillatory states as neuro-phenomenology of consciousness as revealed from patients in vegetative and minimally conscious states. Conscious Cogn. 2012;21(1):149–69.
83. Johansen JW, Sebel PS. Development and clinical application of electroencephalographic bispectrum monitoring. Anesthesiology. 2000;93(5):1336–44.
84. Noirhomme Q, et al. Bispectral index correlates with regional cerebral blood flow during sleep in distinct cortical and subcortical structures in humans. Arch Ital Biol. 2009;147(1–2):51–7.
85. Schnakers C, et al. Diagnostic and prognostic use of bispectral index in coma, vegetative state and related disorders. Brain Inj. 2008;22(12):926–31.
86. Gosseries O, et al. Automated EEG entropy measurements in coma, vegetative state/unresponsive wakefulness syndrome and minimally conscious state. Funct Neurol. 2011;26(1):25–30.
87. Viertio-Oja H, et al. Description of the entropy algorithm as applied in the Datex-Ohmeda S/5 entropy module. Acta Anaesthesiol Scand. 2004;48(2):154–61.
88. Holler Y, et al. Connectivity biomarkers can differentiate patients with different levels of consciousness. Clin Neurophysiol. 2014;125(8):1545–55.
89. Riedner BA, et al. Sleep homeostasis and cortical synchronization: III. A high-density EEG study of sleep slow waves in humans. Sleep. 2007;30(12):1643–57.
90. Bassetti CL, Aldrich MS. Sleep electroencephalogram changes in acute hemispheric stroke. Sleep Med. 2001;2(3):185–94.
91. Crowley K, et al. Differentiating pathologic delta from healthy physiologic delta in patients with Alzheimer disease. Sleep. 2005;28(7):865–70.
92. Cologan V, et al. Sleep in disorders of consciousness. Sleep Med Rev. 2010;14(2):97–105.
93. Landsness E, et al. Electrophysiological correlates of behavioural changes in vigilance in vegetative state and minimally conscious state. Brain. 2011;134(Pt 8):2222–32.

94. Malinowska U, et al. Electroencephalographic profiles for differentiation of disorders of consciousness. Biomed Eng Online. 2013;12(1):109.
95. Cologan, V., et al., Sleep in the unresponsive wakefulness syndrome and minimally conscious state. J Neurotrauma, 2012.
96. Arnaldi D, et al. The prognostic value of sleep patterns in disorders of consciousness in the sub-acute phase. Clin Neurophysiol. 2016;127(2):1445–51.
97. Bekinschtein TA, et al. Can electromyography objectively detect voluntary movement in disorders of consciousness? J Neurol Neurosurg Psychiatry. 2008;79(7):826–8.
98. Habbal D, et al. Volitional electromyographic responses in disorders of consciousness. Brain Inj. 2014;28(9):1171–9.
99. Lesenfants D, et al. Electromyographic decoding of response to command in disorders of consciousness. Neurology. 2016;87(20):2099–107.
100. Wolpaw JR, et al. Brain-computer interfaces for communication and control. Clin Neurophysiol. 2002;113(6):767–91.
101. Schnakers C, et al. Cognitive function in the locked-in syndrome. J Neurol. 2008;255(3): 323–30.
102. Ball LJ, Fager S, Fried-Oken M. Augmentative and alternative communication for people with progressive neuromuscular disease. Phys Med Rehabil Clin N Am. 2012;23(3): 689–99.
103. Bruno MA, et al. Locked-in syndrome in children: report of five cases and review of the literature. Pediatr Neurol. 2009;41(4):237–46.
104. Kubler A, Neumann N. Brain-computer interfaces - the key for the conscious brain locked into a paralyzed body. Prog Brain Res. 2005;150:513–25.
105. Owen AM, et al. Detecting awareness in the vegetative state. Science. 2006;313(5792):1402.
106. Sorger B, et al. Another kind of 'BOLD response': answering multiple-choice questions via online decoded single-trial brain signals. Prog Brain Res. 2009;177:275–92.
107. Sellers EW, Donchin E. A P300-based brain-computer interface: initial tests by ALS patients. Clin Neurophysiol. 2006;117(3):538–48.
108. Sellers EW, Kubler A, Donchin E. Brain-computer interface research at the University of South Florida Cognitive Psychophysiology Laboratory: the P300 speller. IEEE Trans Neural Syst Rehabil Eng. 2006;14(2):221–4.
109. Kübler A. Brain-computer interfaces for communication in paralysed patients and implications for disorders of consciousness. In: Laureys S, Tononi G, editors. The neurology of consciousness. New York: Academic Press; 2009. p. 217–34.
110. Citi L, et al. P300-based BCI mouse with genetically-optimized analogue control. IEEE Trans Neural Syst Rehabil Eng. 2008;16(1):51–61.
111. Yoo SS, et al. Brain-computer interface using fMRI: spatial navigation by thoughts. Neuroreport. 2004;15(10):1591–5.
112. Mugler, E.M., et al., Design and implementation of a P300-based brain-computer interface for controlling an internet browser. IEEE Trans Neural Syst Rehabil Eng, 2010.
113. Sellers, E.W., T.M. Vaughan, and J.R. Wolpaw, A brain-computer interface for long-term independent home use. Amyotroph Lateral Scler, 2010.
114. Lee JH, et al. Brain-machine interface via real-time fMRI: preliminary study on thought-controlled robotic arm. Neurosci Lett. 2009;450(1):1–6.
115. Nijboer F, et al. A P300-based brain-computer interface for people with amyotrophic lateral sclerosis. Clin Neurophysiol. 2008;119(8):1909–16.
116. Donchin E, Spencer KM, Wijesinghe R. The mental prosthesis: assessing the speed of a P300-based brain-computer interface. IEEE Trans Rehabil Eng. 2000;8(2):174–9.
117. Furdea A, et al. An auditory oddball (P300) spelling system for brain-computer interfaces. Psychophysiology. 2009;46(3):617–25.
118. Lule D, et al. Probing command following in patients with disorders of consciousness using a brain-computer interface. Clin Neurophysiol. 2013;124(1):101–6.

119. Combaz A, et al. A comparison of two spelling brain-computer interfaces based on visual P3 and SSVEP in locked-in syndrome. PLoS One. 2013;8(9):e73691.
120. Lesenfants D, et al. An independent SSVEP-based brain-computer interface in locked-in syndrome. J Neural Eng. 2014;11(3):035002.
121. Pfurtscheller G, Lopes da Silva FH. Event-related EEG/MEG synchronization and desynchronization: basic principles. Clin Neurophysiol. 1999;110(11):1842–57.
122. Pfurtscheller G, et al. EEG-based discrimination between imagination of right and left hand movement. Electroencephalogr Clin Neurophysiol. 1997;103(6):642–51.
123. Neuper C, et al. Clinical application of an EEG-based brain-computer interface: a case study in a patient with severe motor impairment. Clin Neurophysiol. 2003;114(3):399–409.
124. Perelmouter J, et al. Language support program for thought translation devices. Automedica. 1999;18:67–84.
125. Pfurtscheller G, et al. 15 years of BCI research at Graz University of Technology: current projects. IEEE Trans Neural Syst Rehabil Eng. 2006;14(2):205–10.
126. Goldfine AM, et al. Determination of awareness in patients with severe brain injury using EEG power spectral analysis. Clin Neurophysiol. 2011;122(11):2157–68.
127. Cruse D, et al. Bedside detection of awareness in the vegetative state. Lancet. 2011; 378(9809):2088–94.
128. Cruse D, et al. The relationship between aetiology and covert cognition in the minimally-conscious state. Neurology. 2012;78(11):816–22.
129. Goldfine AM, et al. Reanalysis of bedside detection of awareness in the vegetative state: a cohort study. Lancet. 2013;381(9863):289–91.
130. Cruse D, et al. Reanalysis of "Bedside detection of awareness in the vegetative state: a cohort study" – authors' reply. Lancet. 2013;381(9863):291–2.
131. Cruse D, et al. Detecting awareness in the vegetative state: electroencephalographic evidence for attempted movements to command. PLoS One. 2012;7(11):e49933.
132. Pan J, et al. Detecting awareness in patients with disorders of consciousness using a hybrid brain-computer interface. J Neural Eng. 2014;11(5):056007.
133. Kennedy PR, Bakay RA. Restoration of neural output from a paralyzed patient by a direct brain connection. Neuroreport. 1998;9(8):1707–11.
134. Kennedy PR, et al. Direct control of a computer from the human central nervous system. IEEE Trans Rehabil Eng. 2000;8(2):198–202.
135. Hochberg LR, et al. Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. Nature. 2012;485(7398):372–5.
136. Hochberg LR, et al. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. Nature. 2006;442(7099):164–71.
137. Brumberg JS, et al. Brain-computer interfaces for speech communication. Speech Commun. 2010;52(4):367–79.
138. Hinterberger T, et al. Voluntary brain regulation and communication with electrocorticogram signals. Epilepsy Behav. 2008;13(2):300–6.
139. Leuthardt EC, et al. A brain-computer interface using electrocorticographic signals in humans. J Neural Eng. 2004;1(2):63–71.
140. Jarosiewicz B, et al. Virtual typing by people with tetraplegia using a self-calibrating intracortical brain-computer interface. Sci Transl Med. 2015;7(313):313ra179.
141. Noirhomme Q, et al. Look at my classifier's result: disentangling unresponsive from (minimally) conscious patients. Neuroimage. 2017;145(Pt B):288–303.
142. Giacino J, et al. The minimally conscious state: definition and diagnostic criteria. Neurology. 2002;58(3):349–53.

Chapter 5
Identifying Covert Cognition in Disorders of Consciousness

Laura E. González-Lara and Adrian M. Owen

Abstract Several recent studies examining different aspects of residual cognitive function in patients with disorders of consciousness (DOC) have shown that multiple tasks and modalities provide the best opportunity for patients to demonstrate covert awareness where it exists. With a wide range of etiologies and comorbidities, this is a very diverse population with variable cognitive and behavioral abilities. Additional challenges include the availability of specific technology as well as the eligibility of individual patients to be assessed with functional magnetic resonance imaging (fMRI) or electroencephalography (EEG). A number of paradigms, in different modalities, have been developed in recent years to assess aspects of residual cognitive function in DOC patients. These include basic auditory, visual, and tactile processing, speech-specific processes, selective attention, executive function, and command following. The results confirm that preserved brain function in DOC may take a wide variety of forms, from basic auditory processing all the way up to preserved command following and communication.

Introduction

Improvements in emergency medicine and critical care have resulted in more patients surviving severe brain injuries. Some of these patients will have a significant functional recovery, albeit with different degrees of physical and/or cognitive impairments. Others will remain in a vegetative state (VS) or a minimally conscious state (MCS), following a period in coma. Assessment of this latter group, patients with disorders of consciousness (DOC), is extremely difficult, and the formal diagnosis relies on subjective interpretation of observed behavior. Moreover, this is a very diverse population of patients with variable cognitive and behavioral abilities that result from a wide range of etiologies and comorbidities. The difficulty of the

L.E. González-Lara • A.M. Owen (✉)
Department of Psychology, The Brain and Mind Institute, The University of Western Ontario, London, ON, Canada, N6A 5B7
e-mail: uwocerc@uwo.ca

C. Schnakers, S. Laureys (eds.), *Coma and Disorders of Consciousness*,
DOI 10.1007/978-3-319-55964-3_5

assessment, coupled with inadequate experience and knowledge due, in part, to the relative rarity of these complex conditions, contributes to an alarmingly high rate of misdiagnosis (up to 43%) in these patient groups [1–3].

In recent years, a number of studies have used functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) to investigate different aspects of cognitive function and search for evidence of covert awareness in patients that are behaviorally nonresponsive at the bedside. In this chapter, we will review some of the EEG and fMRI techniques that have been used in this context, as well as a number of new methodological approaches that have focused on peripheral physiological signals of emotion. Together, these tools have allowed a range of cognitive functions to be probed in DOC, from basic auditory, visual, and tactile processing to speech-specific processes, selective attention, executive function, and command following. By combining different technologies and paradigms, it has been possible to explore the depth and breadth of preserved cognitive function in DOC patients.

The results suggest an urgent need for a reevaluation of the existing diagnostic guidelines for behaviorally nonresponsive patients and for the development and formal inclusion of validated, standardized, neuroimaging procedures into those guidelines.

Identifying Covert Cognition With fMRI

Mental Imagery

Following a severe brain injury, when the request to move a hand or a finger is followed by an appropriate motor response, the diagnosis can change from VS (no evidence of awareness) to MCS (some evidence of awareness). Neuroimaging techniques have provided a means for identifying unique brain activation patterns that can be used as a proxy for behavioral responses to command. For example, if a patient can reliably activate their supplementary motor area in response to being asked to imagine moving their hand, then that neural response carries exactly the same explanatory weight as if the person were actually able to move their hand to command [4–6]. Skeptics may argue that brain responses are somehow less physical, reliable, or immediate than motor responses but, as is the case with motor responses, all of these arguments can be dispelled with careful measurement, replication, and objective verification [7–12]. For example, if a patient who was assumed to be unaware raised his/her hand to command on just one occasion, there would remain some doubt about the presence of awareness given the possibility that this movement was a chance occurrence, coincident with the instruction. However, if that same patient were able to repeat this response to command on ten occasions, there would remain little doubt that the patient was aware. By the same token, if that patient was able to activate his/her supplementary motor area in response to

command (e.g., by being told to imagine hand movements) and was able to do this on every one of ten trials, there would remain little doubt that this patient was consciously aware.

In one large study by Boly and colleagues, 34 healthy volunteers were asked to imagine hitting a tennis ball back and forth to an imaginary coach when they heard the word "tennis" (thereby eliciting vigorous imaginary arm movements) and to imagine walking from room to room in their house when they heard the word "house" (thereby eliciting imaginary spatial navigation) [8]. Imagining playing tennis was associated with robust activity in the supplementary motor area in each and every one of the participants scanned. In contrast, imagining moving from room to room in a house activated the parahippocampal cortices, the posterior parietal lobe, and the lateral premotor cortices, all regions that have been shown to contribute to imaginary, or real, spatial navigation [13]. By simply examining the responses elicited during the imagery tasks, Boly and colleagues were able to decipher which task was being mentally "performed." Moreover, the robustness and reliability of fMRI responses across individuals meant that activity in these regions could be used to confirm that the participants retained the ability to understand instructions and to carry out different mental tasks in response to those instructions and, therefore, were able to exhibit voluntary brain behavior in the absence of any overt action. On this basis, Boly and colleagues argued that, like any other form of action that requires a choice between one of several possible responses, these brain responses are indicative of *awareness*, that is, to say, awareness of the various contingencies that govern the relationship between a given stimulus (in this case, the cue word for one of two possible imagery tasks) and a response (in this case, imagining a type of action). To put it simply, fMRI responses of this sort can be used to measure awareness because awareness is necessary for them to occur [8].

Owen and colleagues used this same logic to demonstrate that a young woman who fulfilled all internationally agreed criteria for VS was, in fact, consciously aware and able to make responses of this sort using her brain activity [7, 9]. The patient, who was involved in a complex road traffic accident and had sustained very severe traumatic brain injuries, had remained entirely unresponsive for a period of 6 months prior to the fMRI scan. During two different scanning sessions, the patient was instructed to perform the two mental imagery tasks described above. In each case, she was asked to imagine playing tennis/moving around the rooms of her home (for 30 s) when she heard the word *tennis/house* and to relax (for 30 s) when she heard the word *relax*. When she was asked to imagine playing tennis, significant activity was observed repeatedly in the supplementary motor area [7] that was indistinguishable from that observed in the healthy volunteers scanned by Boly et al. [8]. Moreover, when she was asked to imagine walking through her home, a significant activity was observed in the parahippocampal gyrus, the posterior parietal cortex, and the lateral premotor cortex which was again indistinguishable from that observed in healthy volunteers [7, 9]. The patient's brain activity was statistically robust, reproducible, task appropriate (enhanced following the "tennis"/"house" cue and returning to baseline following the "relax" cue), sustained over long time

intervals (30 s), and repeated over each 5-min session. On this basis, it was concluded that, despite fulfilling all of the clinical criteria for a diagnosis of VS, this patient retained the ability to understand spoken commands and to respond to them through her brain activity, rather than through speech or movement, confirming that she was consciously aware of herself and her surroundings. In a follow-up study of 23 patients who were behaviorally diagnosed as vegetative, Monti/Vanhaudenhuyse and colleagues showed that four (17%) were able to generate reliable responses of this sort in the fMRI scanner [10].

Owen and Coleman extended the general principles discussed above, by which active mental rehearsal is used to signify awareness, to show that communication of "yes" and "no'" responses was possible using the same approach [14]. Thus, a healthy volunteer was able to reliably convey a "yes" response by imagining playing tennis and a "no'" response by imaging moving around his house, thereby providing the answers to simple questions posed by the experimenters using only his brain activity. This technique was further refined by Monti/Vanhaudenhuyse and colleagues who successfully decoded three "yes" and "no" responses from each of 16 healthy participants with 100% accuracy using only their real-time changes in the supplementary motor area (during tennis imagery) and the parahippocampal place area (during spatial navigation). Moreover, in one traumatic brain injury patient, who had been repeatedly diagnosed as vegetative over a 5-year period, similar questions were posed and successfully decoded using the same approach. Thus, this patient was able to convey biographical information that was not known to the experimenters at the time (but was later verified as factually correct) such as his father's name and the last place that he had visited on vacation before his accident 5 years earlier. In contrast, and despite a re-classification to a minimally conscious state following the fMRI scan, it remained impossible to establish any form of communication with this patient at the bedside [10].

Selective Attention

Although techniques like the ones described above require that the patient engages in rather specific types of mental imagery (playing tennis or moving from room to room through a house), that is not really the main point that allows consciousness to be detected and communication to occur. All that is required to detect consciousness is a reliable indicator that a patient can turn his or her attention to a specific scenario, because this then serves as a "neural proxy" for a physical "response to command." By extension, if it can be shown that the patient can turn his or her attention to two separate scenarios, then communication is possible because those two separate scenarios can be linked to "yes" responses and "no" responses, respectively. Thus, mental imagery is not necessary at all but serves as a simple vehicle for guiding a patient's attention one way or another.

A related and possibly simpler approach to detecting covert awareness after brain injury, therefore, is to target processes that require the willful adoption of "mind-sets" in carefully matched (perceptually identical) experimental and control

conditions. For example, Monti and colleagues presented healthy volunteers with a series of neutral words and alternatively instructed them to just listen, or to count, the number of times a given word was repeated [15]. As predicted, the counting task revealed the frontoparietal network that has been previously associated with target detection and working memory. When tested on this same procedure, a severely brain injured patient produced a very similar pattern of activity, confirming that he could wilfully adopt differential mind-sets as a function of the task conditions and could actively maintain these mind-sets across time. These covert abilities were entirely absent from his documented behavioral repertoire. As in the tennis/spatial navigation examples described earlier, because the external stimuli (a series of words) were identical in the two conditions, any difference in brain activity observed cannot reflect an "automatic" brain response (i.e., one that can occur in the absence of consciousness). Rather, the activity must reflect the fact that the patient has performed a particular action (albeit a "brain action") in response to the stimuli on one (but not the other) presentation; in this sense, the brain response is entirely analogous to a (motor) response to command and should carry the same weight with respect to evidence of awareness.

Naci and colleagues took this general principle even further and developed a novel tool for communicating with nonresponsive patients based on how they selectively directed their attention to sounds while in the fMRI scanner [11, 12]. It is well established that selective attention can significantly enhance the neural representation of attended sounds [16], although most previous studies have focused on group-level changes rather than individual responses that are crucial for work with (individual) brain-injured patients. In the first study by Naci and colleagues, 15 healthy volunteers answered questions (e.g., "Do you have brothers or sisters?") in the fMRI scanner, by selectively attending to the appropriate word ("yes" or "no"), which was played to them auditorily, interspersed with "distractor" stimuli (digits 1–9). Ninety percent of the answers were decoded correctly based on activity changes within the attention network of the brain [11]. Moreover, the majority of volunteers conveyed their answers with less than 3 min of scanning, which represents a significant time saving over the mental imagery methods described above [7–9]. Indeed, a formal comparison between the two approaches revealed improved individual success rates and an overall reduction in the scanning times required to correctly detect responses; 100% of volunteers showed significant task-appropriate activity in the selective attention task, compared to 87% in the motor imagery tasks. This result is consistent with previous studies showing that a proportion of healthy volunteers do not produce reliable brain activation during mental imagery tasks [8].

In a follow-up study, Naci and Owen used the same approach to test for residual conscious awareness and communication abilities in three behaviorally nonresponsive, brain-injured patients [12]. As in the previous study of healthy participants, the patients had to either "count" or "relax" as they heard a sequence of words. The word *count* at the beginning of the sequence instructed the patient to count the occurrences of a target word (*yes* or *no*), while the word *relax* instructed them to relax and ignore the sequence of words. Reliable activity increases in the attention network of the brain after the word *count* relative to the word *relax* were taken as evidence of command following. All three patients (two of whom were diagnosed

as being in a MCS and one as being in a VS) were able to convey their ability to follow commands inside the fMRI scanner by following the instructions in this way. In a stark contrast, extremely limited or a complete lack of behavioral responsivity was observed in repeated bedside assessments of all three patients. These results confirm that selective attention is an appropriate vehicle for detecting covert awareness in some behaviorally nonresponsive patients who are presumed to mostly or entirely lack any cognitive abilities whatsoever [12].

In subsequent fMRI sessions, communication was attempted with two of the patients in that study [12]. During these sessions, instead of an instruction (to count or relax), a binary question (e.g., "Is your name John?") preceded each sound sequence. Thus, each patient then had to wilfully choose which word to attend to (count) and which to ignore, depending on which answer they wished to convey to the specific question that had been asked. Using this method, the two patients (one diagnosed as MCS and one diagnosed as VS) were able to use selective attention to repeatedly communicate correct answers to questions that were posed to them by the researchers [12]. In the absence of external cues as to which word the patient was attending to, the functional brain activation served as the only indicator of the patient's intentions—and in both cases led to the correct answers being decoded. For example, when asked "Are you in a supermarket?" one patient showed significantly more activation for "no" than "yes" sequences in a network of brain areas that had been previously activated when that patient was focusing attention on external cues. Conversely, when asked "Are you in a hospital?" the patient showed significantly more activation for "yes" than "no" sequences in those same brain regions. Despite his diagnosis (VS for 12 years), the fMRI approach allowed this patient to establish interactive communication with the research team in four different fMRI sessions. The patient's brain responses within specific regions were remarkably consistent and reliable across two different scanning visits, 5 months apart, during which the patient maintained the long-standing VS diagnosis. For all of the four questions, the patient produced a robust neural response and was able to provide the correct answers with 100% accuracy. The patient's brain activity in the communication scans not only further corroborated that he was, indeed, consciously aware but also revealed that he had far richer cognitive reserves than could be assumed based on his clinical diagnosis. In particular, beyond the ability to pay attention, these included autobiographical knowledge and awareness of his location in time and space [12].

Identifying Covert Cognition Through EEG

Performing fMRI in severely brain-injured patients is enormously challenging; in addition to considerations of cost and scanner availability, the physical stress incurred by patients as they are transferred to a suitably equipped fMRI facility may be significant. Movement artifacts often occur in imaging datasets from patients who are unable to remain still, while metal implants, including plates and

pins which are common in many traumatically injured populations, may rule out fMRI altogether. EEG measures the activity of groups of cortical neurons from scalp electrodes and is far less expensive than fMRI, both in terms of initial cost and maintenance. EEG recordings are unaffected by any resident metallic implants and, perhaps most importantly, can be used at the bedside [17]. In brain-injured patients, EEG recordings are typically made in the acute period and allow for broad assessments of cortical damage including the occurrence of brain death. However, uncertainty about the causes of abnormal raw EEG patterns (i.e., damage to the cortex itself or to subcortical structures which influence cortical activity) provides challenges for its use as a more precise tool for the assessment of awareness [18].

Motor imagery produces clearly distinguishable modulation of EEG sensorimotor rhythms similar to those seen during motor execution and has been the basis of several recent attempts to detect conscious awareness after severe brain injury [19, 20]. For example, Cruse and colleagues developed a novel EEG-based classification technique in which two mental imagery responses (squeezing the right hand or squeezing the toes) were successfully decoded offline in 9 out of 12 healthy individuals with accuracy rates varying between 60 and 91% [21]. The same approach was then used to attempt to detect evidence of command following the absence of any overt behavior in a group of 16 patients who met the internationally agreed criteria for a diagnosis of VS. Three of these patients (19%, two traumatic brain injury and one nontraumatic brain injury) were repeatedly and reliably able to generate appropriate EEG responses to the two distinct commands ("squeeze your right hand" or "squeeze your toes"), despite being behaviorally entirely unresponsive, indicating that they were aware and following the task instructions. Indeed, on the basis of such data, far broader conclusions about residual cognition can be drawn. For example, performance of this complex task makes multiple demands on many cognitive functions, including sustained attention (over 90-s blocks), response selection (between the two imagery tasks), language comprehension (of the task instructions), and working memory (to remember which task to perform across multiple trials within each block), all aspects of "top-down" cognitive control that are usually associated with—indeed, could be said to characterize—normal conscious awareness [22].

In a follow-up study, 23 minimally conscious state patients (15 traumatic brain injury and 8 nontraumatic brain injury) completed the same motor imagery EEG task. Consistent and robust responses to command were observed in the EEG of 22% of the minimally conscious state patients (5/23) [23]. Etiology had a significant impact on the ability to successfully complete this task, with 33% of traumatic patients (5/15) returning positive EEG outcomes, compared with none of the nontraumatic patients (0/8). However, the link between etiology and projected neuroimaging outcomes remains poorly understood and must be interpreted with caution where individual patients are concerned, as patients in both traumatic and nontraumatic groups vary widely in etiologies, neuropathology, and clinical features. Indeed, in some cases, nontraumatic brain-injured patients have returned positive outcomes, including one of the three patients in the aforementioned study [21].

In a more recent study, Cruse and colleagues refined their EEG approach using a simpler and more clinically viable paradigm that required participants to actually try to move their hands, and, unlike the two previous studies [21, 23], 100% of the healthy volunteers showed reliable event-related desynchronization and event-related synchronization responses [24]. Moreover, in one of the patients studied previously by Naci and Owen [12], who had been repeatedly diagnosed as vegetative for 12 years, reliable modulations of sensorimotor beta rhythms were observed following commands to try to move, and these could be classified significantly at a single-trial level [24]. This patient is the first published case of a clinically vegetative patient in whom awareness has been demonstrated using two independent imaging methods (fMRI and EEG) in the absence of any supportive evidence from clinical (behavioral) examination [6].

Is it possible that appropriate patterns of activity could be elicited in patients like this in the absence of awareness? Could they somehow reflect an "automatic" response to aspects of the task instructions, such as the words "right hand" and "toes," and not a conscious and overt "action" on the part of the patient? This is extremely unlikely for a number of reasons. First, the task instructions were delivered once at the beginning of each block of tones that signaled the time to begin each imagery trial. Any "automatic" response to the previously presented verbal instruction would then have to abate and recur in synchrony with these tones/cues that carried no information in themselves about the task to be performed. Indeed, 75% of the healthy control participants tested in the study by Cruse and colleagues returned positive EEG outcomes when completing this motor imagery task. However, when these same individuals were instructed *not* to follow the commands—i.e., not to engage in motor imagery—not one participant returned a positive EEG outcome [21]. Evidently, any automatic brain responses generated by listening to the instructions are not sufficient for significant task performance; rather, an act of consistently timed, volitional command following is required. In this context then, it is clear that successful performance of these EEG tasks represents a significant cognitive feat, not only for those patients who were presumed to be vegetative but also for healthy control participants. That is to say, to be deemed successful, each respondent must have consistently generated the requested mental states to command for a prolonged period of time within each trial and must have consistently done so across numerous trials. Indeed, one behaviorally vegetative patient was able to produce EEG responses that were classified with a success rate of 78% [21]. In other words, consistently appropriate EEG responses were generated across approximately 100 trials. Conversely, when assessed behaviorally using accepted standard clinical measures that were administered by experienced specialist teams, none of these patients exhibited any signs of awareness, including visual fixation, visual pursuit, or localization to pain. These results demonstrate that consistent responses to command—a reliable and universally accepted indicator that a patient is not vegetative—need not be expressed behaviorally at all but, rather, can be determined accurately on the basis of EEG responses [24].

The success of recent EEG techniques for detecting awareness in nonresponsive patients [21, 23, 24] paves the way for the development of a true "brain-computer interface" (BCI) [25]—or simple, reliable communication devices—in this patient group. It seems likely that such devices will provide a form of external control and communication based on mappings of distinct mental states—for example, attempting right-hand movements to communicate "yes" and toe movements to communicate "no" [24]. Indeed, the degrees of freedom provided by EEG have the potential to take this beyond the sorts of binary responses that have worked well using fMRI [6, 10–12], to allow methods of communication that are far more functionally expressive. The development of techniques for the real-time classification of these forms of mental imagery [21, 23, 24] will open the door for a routine two-way communication with some of these patients, ultimately allowing them (within the constraints of BCI technologies) to share information about their inner worlds, experiences, and needs.

Emerging Approaches

False-negative findings in functional neuroimaging studies are common, even in healthy volunteers, and they present particular difficulties in this patient population. For example, a patient may fall asleep during the scan or may not have properly heard or understood the task instructions, leading to an erroneous negative result. Indeed, in the study by Monti/Vanhaudenhuyse and colleagues, no wilful fMRI responses were observed in 19 of 23 patients—whether these are *true* negative findings (i.e., those 19 patients were indeed vegetative) or *false-negative* findings (i.e., some of those patients were conscious, but this was not detected on the day of the scan) cannot be determined [10]. Accordingly, negative fMRI and EEG findings in patients should never be used as evidence for impaired cognitive function or lack of awareness.

Furthermore, inconsistent responses, either through behavioral or neuroimaging assessments, add to the challenge of assessing patients who may have varying degrees of awareness over time. In the first study to evaluate convergence and divergence of fMRI and EEG findings in this group of patients, Gibson and colleagues concluded that the application of multiple paradigms gives patients the best opportunity for demonstrating covert awareness [26]. In that study, six patients were evaluated using standard clinical behavioral assessments, EEG, and fMRI. During the fMRI assessments, patients were asked to perform either a motor imagery task (playing tennis) or a spatial navigation imagery task (moving through a familiar place) as previously described [6, 7, 10, 27]. During the EEG assessments, two types of motor imagery were used, a conventional one (i.e., squeezing a hand) [21, 24] and a familiar one (an action the patients had experience with prior to their injury) [28]. Event-related desynchronizations were only observed in some of the patients during the conventional imagery task but were not produced by any patients during the familiar task. One patient demonstrated command following using both

fMRI and EEG. Two patients showed significant and anatomically appropriate fMRI activation during the spatial navigation task, although there was no evidence of activation during the motor imagery tasks with either fMRI or EEG. Conversely, one patient produced EEG event-related desynchronizations during conventional motor imagery task, but no significant activation was observed during any of the fMRI tasks. In the last two patients, there was no evidence of reliable activation during any of the tasks using either fMRI or EEG [26]. The results of this study emphasize the importance of using a battery of assessments to investigate covert awareness. The exact source of the variability observed in this group is not entirely clear, although the locus of injury in each patient is a likely factor, as is daily variations in arousal level and motivation. By using multiple tools, all patients have the best opportunity to demonstrate residual cognitive abilities (where they exist) via one or more of these methods.

The approaches discussed so far all illustrate the use of active (e.g., wilful) tasks in the assessment of covert awareness after serious brain injury. The neural responses required are not produced *automatically* by the eliciting stimulus but, rather, depend on time-dependent and sustained responses generated by the participants themselves. Such behavior (albeit neural "behavior") provides a proxy for a motor action and is, therefore, an appropriate vehicle for reportable awareness [29].

To further investigate alternative approaches to this problem, Gibson and colleagues recently developed a paradigm that does not use visual stimuli nor depend solely on auditory stimuli [30]. They assessed somatosensory-selective attention by eliciting steady-state evoked potentials (SSEP) and measuring event-related potentials (ERP) in 14 patients using a vibrotactile stimulus. A hierarchical approach was used to probe SSEP, bottom-up attention (P3a ERP), and top-down attention (P3b ERP) using an oddball paradigm; the results were compared to those obtained through the fMRI motor imagery, spatial navigation [4, 5, 7, 8, 10], and selective auditory attention [11, 12] paradigms, described above. Gibson and colleagues found SSEPs in all 14 patients, indicating a basic sensory response to the vibrotactile stimulus. Furthermore, bottom-up attention ERPs (P3a) were detected in eight patients. While top-down ERPs (P3b) were not detected in any of the patients; all of the patients who showed P3a effects also demonstrated evidence of command following, either through behavioral or fMRI responses (Fig. 5.1). The relationship between P3a and command following suggests an overlap of the neural attention networks responsible for these different types of output. However, the fact that the P3a can be elicited without the patient being required to follow any instructions suggests that this paradigm may serve as a passive assessment with lower cognitive demands than active orienting of attention.

Passive Paradigms

While "active" paradigms have proven themselves to be an effective means for assessing residual awareness in some nonresponsive patients, it remains likely that many patients will lack the necessary cognitive resources for carrying out these

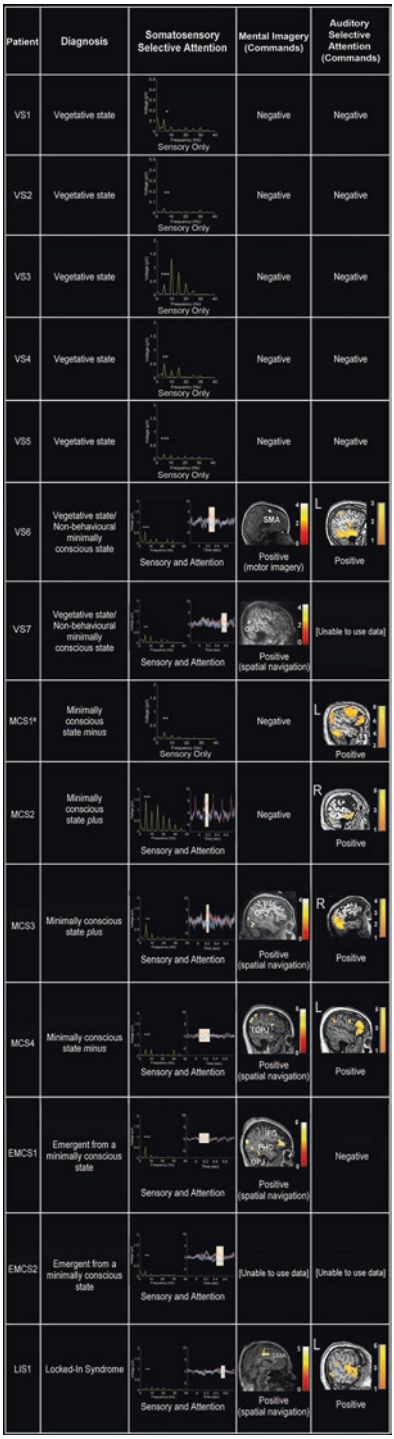

Fig. 5.1 Fourteen patients with diagnosis of VS, MCS, EMCS, and LIS were assessed using a vibrotactile stimulus. The results were compared to those obtained through the fMRI motor imagery, spatial navigation, and selective auditory attention paradigms. SSEPs were present in all 14 patients. Bottom-up attention ERPs (P3a) were detected in eight patients who also demonstrated evidence of command following either through behavioral or fMRI responses. Reprinted from Gibson RM, Chennu S, Fernández-Espejo D, Naci L, Owen AM, and Cruse D. Somatosensory attention identifies both overt and covert awareness in disorders of consciousness. Ann Neurol 80(3):412–23 2016, with permission from John Wiley & Sons, Inc.

tasks in the scanner and will therefore fail to exhibit signs of awareness even when it may exist. To further address this issue, Naci and colleagues have used a richly evocative stimulus—a highly suspenseful movie—to capture attention naturally in the absence of structured instruction [31]. In order to establish whether some DOC patients experience the world in a way that is similar to healthy individuals (despite their outward appearance), Naci and colleagues investigated whether a common neural basis can account for how different individuals form similar conscious experiences, and if so, whether it could be used to interpret those experiences without recourse to self-report in behaviorally nonresponsive patients. They reasoned that executive function, in particular, might provide an empirical window by which the cognitive aspect of human conscious experience can be quantified. By their very nature, engaging movies are designed to give viewers a shared conscious experience driven, in part, by the recruitment of similar executive processes, as each viewer continuously integrates their observations, analyses, and predictions while filtering out any distractions, leading to an ongoing involvement in the movie's plot [31].

When healthy participants viewed a highly engaging short movie by Alfred Hitchcock—the so-called Master of Suspense—in the fMRI scanner, they displayed highly synchronized brain activity in supramodal frontal and parietal regions, which support executive function [32, 33]. The movie's executive demands, assessed quantitatively with a dual-task procedure [34] in an independent group, predicted activity in frontal and parietal regions of the healthy participants, who had watched the movie without a secondary task in the scanner. Also, the movie's suspense ratings, provided by a third independent healthy group, demonstrated that individual participants had a similar qualitative experience of the movie, which also predicted activity in the frontal and parietal regions. Together, these results suggested that the movie's executive demands drove brain activity in frontal and parietal regions and, furthermore, that the synchronization of this activity across individuals underpinned their similar experience. By extension, the degree to which each individual's frontoparietal brain activity could be predicted from the rest of the group's represented a reliable neural index of how similar his/her cognitive experience was to the others'.

Naci and colleagues then applied this approach to two entirely behaviorally nonresponsive patients with unknown levels of consciousness, in order to examine and quantify their experience of the world. fMRI data was acquired from the two patients, as they freely viewed the same Hitchcock movie [31]. One patient, who had remained behaviorally nonresponsive for a 16-year period prior to scanning, demonstrated a highly similar brain response to that of the three independent control groups. The patient's brain activity in frontal and parietal regions was tightly synchronized with the healthy participants' over time, and crucially, it reflected the executive demands of specific events in the movie, as measured both quantitatively and qualitatively in healthy individuals. This suggested that the patient could continuously engage in complex thoughts about real-world events unfolding over time and, thus, that he was consciously aware. Moreover, the patient's brain response suggested that his conscious experience was highly similar to that of each and every healthy participant, including his moment-to-moment perception of the movie content, as well as his

executive engagement with its plot. These processes are likely to include updating the contents of working memory (e.g., to follow the plot), relating events in the movie to past experiences (e.g., to appreciate that a gun is a dangerous weapon), and coding the foreshadowing cues (i.e., events that might have future relevance to the plot) characteristic of movies of this type [31]. No such responses in frontal and parietal regions were observed in the second patient, despite similar behavioral and clinical profiles.

A problem with this approach is that sustained visual fixation and tracking are not preserved in most patients who have a VS diagnosis [35]. To address this challenge, Naci and colleagues developed an auditory-only task using the composite soundtrack from an early and suspenseful scene from the movie "Taken" to investigate executive function [36]. In this short audio story, both speech and other sound effects are important for the development of the plot. Like the previous study, this auditory paradigm does not require that participants follow instructions but engage attention naturally through lifelike sounds and speech. Highly correlated activity patterns, including frontoparietal regions, were recorded across the brain of 15 healthy individuals suggesting that this audio-story paradigm is suitable for investigating executive function in behaviorally nonresponsive patients who may have impaired vision but preserved auditory function [36]. Indeed, in a remarkable case of recovery from the vegetative state, a patient who had been vegetative for several months following an anoxic brain injury produced responses in frontal and parietal regions during this auditory task that were very similar to those of healthy controls (Fig. 5.2). At the time, this data was the only information available to the investigators that the patient was anything other than vegetative. Yet 7 months later, the patient had recovered to the point that he was able to talk and walk (with assistance) and was preparing to return to school. At that time, he was able to report a remarkably detailed account of his evaluation 7 months earlier (when he had appeared to

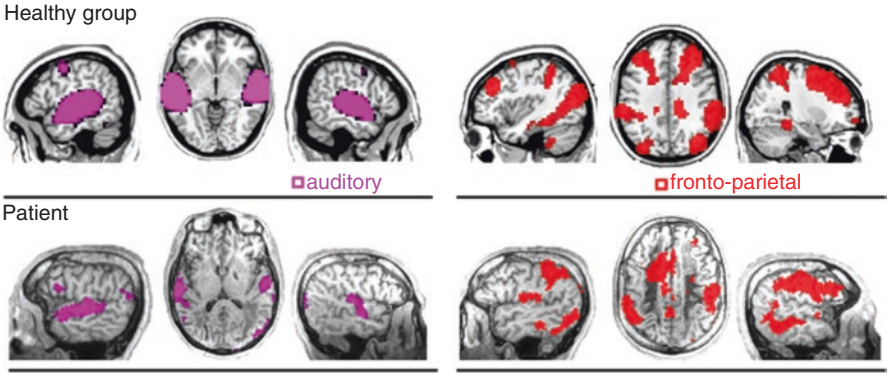

Fig. 5.2 (*Top row*) Fifteen healthy volunteers show highly correlated activity patterns, including frontoparietal regions while listening to a suspenseful short audio story. (*Bottom row*) A patient, who at the time the data was acquired had a VS diagnosis though later had a remarkable recovery, produced responses in frontal and parietal regions very similar to those of healthy controls

be entirely vegetative), including details of the plot of the movie soundtrack that he had been exposed to during the fMRI scan.

Fiacconi and Owen have recently used an entirely different approach to examine peripheral physiological signals of emotional functioning in 36 healthy controls and 2 behaviorally nonresponsive patients [37]. They measured facial electromyography (EMG) while participants listened to sentences, half of which were jokes and half of which were non-jokes. Greater zygomatic and reduced corrugator muscle activity was observed when comparing jokes to non-jokes in 31 of the healthy volunteers (86%). Using EMG to detect peripheral changes in this way has clinical and practical advantages over techniques like fMRI and EEG, as it is relatively inexpensive and very portable. Accordingly, one of the patients, who had been behaviorally nonresponsive for almost 17 years, exhibited an increased zygomatic response and decreased corrugator response, similar to healthy volunteers, when comparing jokes and non-jokes (Fig. 5.3). Because high-level language processes are required to

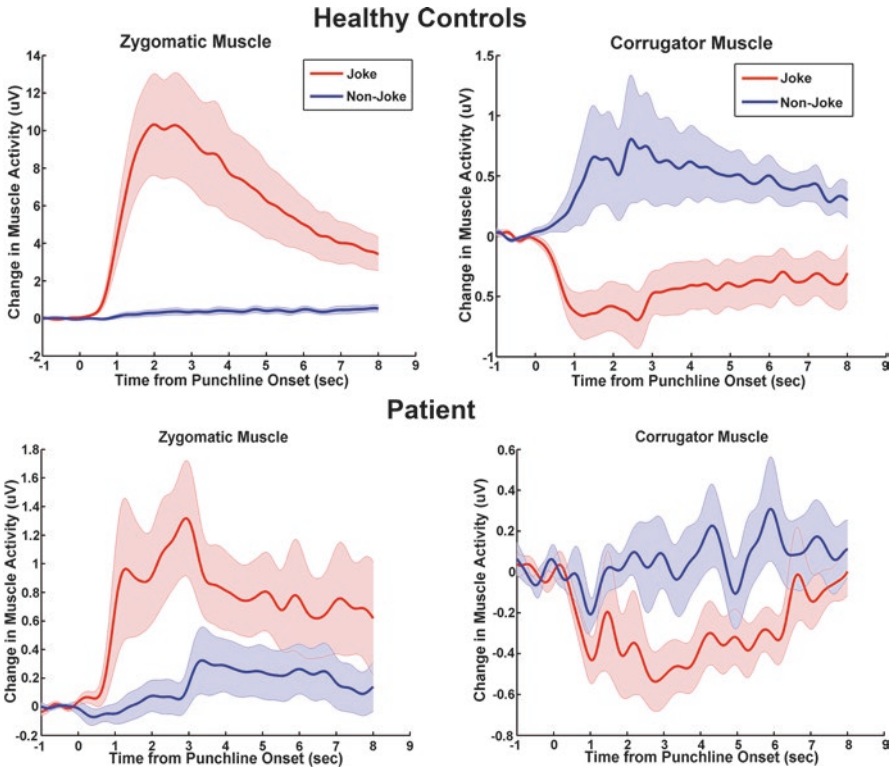

Fig. 5.3 (*Top row*) Facial EMG of healthy participants shows greater zygomatic and reduced corrugator muscle activity when comparing jokes to non-jokes. (*Bottom row*) A patient, who had been behaviorally nonresponsive for almost 17 years, exhibited an increased zygomatic response and decreased corrugator response, similar to healthy volunteers, when comparing jokes and non-jokes. Adapted from Fiacconi CM and Owen AM. Using facial electromyography to detect preserved emotional processing in disorders of consciousness: A proof-of-principle study. Clin Neurophysiol 127(9):3000–6 2016, with permission from Elsevier

"get" a joke, the peripheral changes in muscle activity observed can be used to confirm that both speech perception and language comprehension are preserved in behaviorally nonresponsive patients. Moreover, the preservation of the zygomatic muscle responses to jokes implies that the emotional processes involved in appreciating humor remain intact despite the patient's brain injury.

Implications

Diagnostic Implications

An obvious clinical consequence of the emergence of novel neuroimaging techniques that permit the identification of covert awareness and communication in the absence of any behavioral response is the possibility of improved diagnosis after severe brain injury. It is notable that in one of the cases described above, the patient was repeatedly and rigorously assessed by experienced teams and showed no behavioral sign of awareness on any of these occasions—indeed, this continued to be the case even after awareness had been established unequivocally with both fMRI and EEG [6, 12, 24]. Technically, however, he was not *misdiagnosed* (as VS), in the sense that any error of judgment was made, because the accepted diagnostic criteria are based on behavior, and no behavioral marker of awareness was missed. Nevertheless, the existing criteria did not accurately capture his actual state of awareness, and in this sense, his VS diagnosis was clearly incorrect. What then is the appropriate diagnostic label for such patients and who can follow commands with a measurable brain response but physically remain entirely nonresponsive? The term "nonbehavioral minimally conscious state" has been suggested [38], although because attention, language comprehension, and working memory are demonstrably preserved in these patients, we have argued that "minimally conscious" does not adequately describe their residual cognitive abilities [6, 12]. Indeed, the patient described above was consistently and reliably able to communicate (using fMRI), which places him well beyond the diagnostic criteria describing the minimally conscious state. The term "functional locked-in syndrome" has also been proposed for patients who demonstrate consistent and reliable communication using solely adjunctive technologies [39, 40]. In its classical clinical presentation, "locked-in syndrome" refers to patients who are left with only vertical eye movements and/or blinking, which often permits rudimentary communication. Cognitive function, however, is generally fully preserved, at least in those cases where the lesion is limited to the ventral pons [41]. Patients like the one described here are clearly "locked in" in the general sense of the term but do not have many of the same neuropathological and clinical features of the classic locked-in syndrome. Moreover, at present, there is still considerable uncertainty about the full extent of residual cognitive function in such patients and, thus, about the suitability of the term "functional locked-in syndrome." This is precisely the sort of question that can be explored with neuroimaging techniques.

Decision-Making

An obvious application for approaches of this sort is to begin to involve some of these patients in the decision-making processes involved in their own therapeutic care and management. To date, this has only been achieved successfully in one patient, who had been repeatedly diagnosed as vegetative for 12 years following a traumatic brain injury [6]. The patient was a male who, at the age of 26, had suffered a severe closed head injury in a motor vehicle accident. On admission to a hospital, he had a Glasgow Coma Scale [42] score of 4, meaning that he was unable to open his eyes or produce any sound, and his only response was extension to painful stimulation. Over the next 12 years, the patient was assessed regularly by experienced neurologists and multidisciplinary teams, and throughout this period, his behavior remained consistent with the internationally accepted criteria for the VS. Indeed, over a 14-month period, a total of 20 standardized behavioral assessments were performed by a multidisciplinary team, at different times of the day and in different postural positions, using the Coma Recovery Scale – Revised [43], and his diagnosis was unchanged throughout. Twelve years and 2 months after his accident, the patient was first scanned using the fMRI mental imagery approach described before [7, 10]. The patient was able to provide correct answers to multiple externally verifiable questions, including his own name, his whereabouts, the name of his personal support worker (who he had only encountered in the years following his accident), the current date, and other basic factual information (e.g., whether a banana is yellow). Two non-verifiable questions were then posed, including one pertaining to his care preferences (e.g., whether he liked watching (ice) hockey games on TV) and another to details about his current clinical condition (e.g., whether he was in any physical pain). Within the time constraints of the scanning visits, the majority of responses to these questions were verified in independent sessions that posed the reverse questions (e.g., "Is your name Mike?" vs. "Is your name Scott?"). In all, answers to 12 different questions were obtained across several sessions, despite the fact that the patient remained entirely physically nonresponsive at the bedside [6].

Schnakers developed a standardized neuropsychological assessment for locked-in syndrome that uses simple eye movements as responses (in most cases to provide "yes"/"no" answers to questions) [41]. There is no technical or theoretical reason why a similar approach could not be used with neuroimaging tools in entirely nonresponsive patients, although the data would take considerably longer to acquire. To this end, Hampshire and colleagues used fMRI to assess complex logical reasoning ability in a patient who was assumed to be in a vegetative state [44]. Adapting a verbal reasoning paradigm from Baddeley [45], Hampshire and colleagues presented participants with statements describing the ordering of two objects: a face and a house. Participants were instructed to deduce which of the objects was in front and to visualize the object in their mind. For example, if they heard the statement "the face is not followed by a house," the correct answer would be "house." Conversely, if they heard "the face precedes the house," the correct answer would be "face." The patient engaged the same brain regions as healthy individuals in response

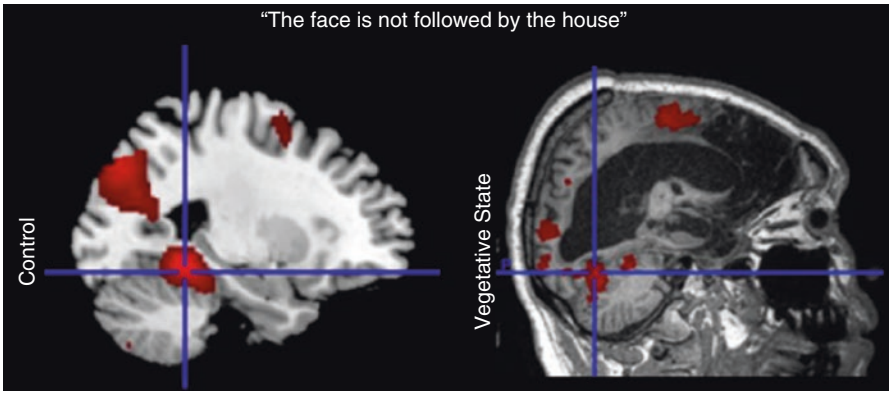

Fig. 5.4 A patient (*right*) engaged the same brain regions as healthy individuals (*left*) in response to reasoning task demand during a verbal reasoning paradigm to assess complex logical reasoning

to the reasoning task demand (Fig. 5.4). This result was consistent with the patient's positive outcome in the fMRI command-following task [7, 8] and suggested that, despite the long-standing clinical diagnosis of vegetative state, he was not only consciously aware but, critically, retained capacity for higher-order cognition, in particular, for solving logically complex verbal problems.

In summary, using neuroimaging techniques, we are beginning to determine not only whether any given patient is conscious but also to infer what the contents of that conscious experience might actually be, thus revealing important practical and ethical implications for the patient's standard of care and quality of life [46].

Conclusions

In the last few years, neuroimaging methods—most notably fMRI and EEG—have been brought to bear on one of the most complex and challenging questions in clinical medicine, that of detecting residual cognitive function, and even covert awareness, in patients who have sustained severe brain injuries. The results demonstrate that responses need no longer be *physical* responses in the traditional sense (e.g., the blink of an eye or the squeezing of a hand) but can now include responses that occur entirely within the brain itself. The recent use of reproducible and robust task-dependent fMRI responses as a form of "communication" in patients who are assumed to be vegetative [6, 10, 12] represents an important milestone in this process. In some cases, these patients have been able to communicate information that was not known by the experimenters at the time, yet could be independently verified later, as being factually correct and true [10, 12]. More importantly perhaps, in one case, a patient has used these methods to answer clinically and therapeutically relevant questions (including "Are you in any pain?") that could not be answered in

any other way, including via third party [6]. Further refinement of other tools such as EEG and EMG, which are relatively more portable and cost effective, will undoubtedly move this field even closer to a true brain-computer interface. Ultimately, this development may increase the opportunities for communication in behaviorally nonresponsive patients with covert awareness and potentially allow them to participate in quality-of-life decisions [46].

Acknowledgments This work was funded by generous awards to Adrian M. Owen from the Canada Excellence Research Chair (CERC) Program, the Canadian Institutes of Health Research (CIHR), the Natural Sciences and Engineering Research Council of Canada (NSERC), the Canada First Research Excellence Fund (CFREF), and the James S. McDonnell Foundation.

References

1. Childs NL, Mercer WN, Childs HW. Accuracy of diagnosis of persistent vegetative state. Neurology. 1993;43(8):1465–7.
2. Andrews K, Murphy L, Munday R, Littlewood C. Misdiagnosis of the vegetative state: retrospective study in a rehabilitation unit. BMJ. 1996;313(7048):13–6.
3. Schnakers C, Vanhaudenhuyse A, Giacino J, Ventura M, Boly M, Majerus S, et al. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. BMC Neurol. 2009;9:35.
4. Owen AM, Coleman MR. Functional neuroimaging of the vegetative state. Nat Rev Neurosci. 2008;9(3):235–43.
5. Owen AM. Detecting consciousness: a unique role for neuroimaging. Annu Rev Psychol. 2013;64:109–33.
6. Fernández-Espejo D, Owen AM. Detecting awareness after severe brain injury. Nat Rev Neurosci. 2013;14(11):801–9.
7. Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD. Detecting awareness in the vegetative state. Science. 2006;313(5792):1402.
8. Boly M, Coleman MR, Davis MH, Hampshire A, Bor D, Moonen G, et al. When thoughts become action: an fMRI paradigm to study volitional brain activity in non-communicative brain injured patients. NeuroImage. 2007;36(3):979–92.
9. Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Jolles D, et al. Response to comments on "detecting awareness in the vegetative state". Science. 2007;315(5816):1221–1.
10. Monti MM, Vanhaudenhuyse A, Coleman MR, Boly M, Pickard JD, Tshibanda L, et al. Willful modulation of brain activity in disorders of consciousness. N Engl J Med. 2010;362(7):579–89.
11. Naci L, Cusack R, Jia VZ, Owen AM. The brain's silent messenger: using selective attention to decode human thought for brain-based communication. J Neurosci. 2013;33(22):9385–93.
12. Naci L, Owen AM. Making every word count for nonresponsive patients. JAMA Neurol. 2013;70(10):1235–41.
13. Aguirre GK, Detre JA, Alsop DC, D'Esposito M. The parahippocampus subserves topographical learning in man. Cereb Cortex. 1996;6(6):823–9.
14. Owen AM, Coleman MR. Detecting awareness in the vegetative state. Ann N Y Acad Sci. 2008;1129:130–8.
15. Monti MM, Coleman MR, Owen AM. Executive functions in the absence of behavior: functional imaging of the minimally conscious state. Prog Brain Res. 2009;177:249–60.
16. Bidet-Caulet A, Fischer C, Besle J, Aguera P-E, Giard M-H, Bertrand O. Effects of selective attention on the electrophysiological representation of concurrent sounds in the human auditory cortex. J Neurosci. 2007;27(35):9252–61.

17. Vaughan TM, McFarland DJ, Schalk G, Sarnacki WA, Krusienski DJ, Sellers EW, et al. The Wadsworth BCI research and development program: at home with BCI. IEEE Trans Neural Syst Rehabil Eng. 2006;14(2):229–33.
18. Kulkarni VP, Lin K, Benbadis SR. EEG findings in the persistent vegetative state. J Clin Neurophysiol. 2007;24(6):433–7.
19. Wolpaw JR, McFarland DJ, Neat GW, Forneris CA. An EEG-based brain-computer interface for cursor control. Electroencephalogr Clin Neurophysiol. 1991;78(3):252–9.
20. Cincotti F, Mattia D, Babiloni C, Carducci F, Salinari S, Bianchi L, et al. The use of EEG modifications due to motor imagery for brain-computer interfaces. IEEE Trans Neural Syst Rehabil Eng. 2003;11(2):131–3.
21. Cruse D, Chennu S, Chatelle C, Bekinschtein TA, Fernández-Espejo D, Pickard JD, et al. Bedside detection of awareness in the vegetative state: a cohort study. Lancet. 2011;378(9809):2088–94.
22. Naccache L. Psychology. Is she conscious? Science. 2006;313(5792):1395–6.
23. Cruse D, Chennu S, Chatelle C, Fernández-Espejo D, Bekinschtein TA, Pickard JD, et al. Relationship between etiology and covert cognition in the minimally conscious state. Neurology. 2012;78(11):816–22.
24. Cruse D, Chennu S, Fernández-Espejo D, Payne WL, Young GB, Owen AM. Detecting awareness in the vegetative state: electroencephalographic evidence for attempted movements to command. PLoS One. 2012;7(11):e49933.
25. Birbaumer N. Breaking the silence: brain-computer interfaces (BCI) for communication and motor control. Psychophysiology. 2006;43(6):517–32.
26. Gibson RM, Fernández-Espejo D, Gonzalez-Lara LE, Kwan BY, Lee DH, Owen AM, et al. Multiple tasks and neuroimaging modalities increase the likelihood of detecting covert awareness in patients with disorders of consciousness. Front Hum Neurosci. 2014;8:950. http://journal.frontiersin.org/article/10.3389/fnhum.2014.00950/abstract
27. Fernández-Espejo D, Norton L, Owen AM. The clinical utility of fMRI for identifying covert awareness in the vegetative state: a comparison of sensitivity between 3T and 1.5T. Zhang N, editor. PLoS One. 2014;9(4):e95082.
28. Gibson RM, Chennu S, Owen AM, Cruse D. Complexity and familiarity enhance single-trial detectability of imagined movements with electroencephalography. Clin Neurophysiol. 2014;125(8):1556–67.
29. Zeman A. The problem of unreportable awareness. Prog Brain Res. 2009;177:1–9.
30. Gibson RM, Chennu S, Fernández-Espejo D, Naci L, Owen AM, Cruse D. Somatosensory attention identifies both overt and covert awareness in disorders of consciousness. Ann Neurol. 2016;80(3):412–23.
31. Naci L, Cusack R, Anello M, Owen AM. A common neural code for similar conscious experiences in different individuals. Proc Natl Acad Sci U S A. 2014;111(39):14277–82.
32. Barbey AK, Colom R, Solomon J, Krueger F, Forbes C, Grafman J. An integrative architecture for general intelligence and executive function revealed by lesion mapping. Brain. 2012;135(4):1154–64.
33. Duncan J. The multiple-demand (MD) system of the primate brain: mental programs for intelligent behaviour. Trends Cogn Sci. 2010;14(4):172–9.
34. Robertson IH, Manly T, Andrade J, Baddeley BT, Yiend J. "Oops!": performance correlates of everyday attentional failures in traumatic brain injured and normal subjects. Neuropsychologia. 1997;35(6):747–58.
35. Medical aspects of the persistent vegetative state (1). The Multi-Society Task Force on PVS. N Engl J Med. 1994;330(21):1499–508.
36. Naci L, Sinai L, Owen AM. Detecting and interpreting conscious experiences in behaviorally non-responsive patients. Neuroimage. 2017;145(Pt B):304–13. http://linkinghub.elsevier.com/retrieve/pii/S1053811915010964
37. Fiacconi CM, Owen AM. Using facial electromyography to detect preserved emotional processing in disorders of consciousness: a proof-of-principle study. Clin Neurophysiol. 2016;127(9):3000–6.

38. Fins JJ, Schiff ND. Shades of gray: new insights into the vegetative state. Hast Cent Rep. 2006;36(6):8.
39. Giacino JT, Schnakers C, Rodriguez-Moreno D, Kalmar K, Schiff N, Hirsch J. Behavioral assessment in patients with disorders of consciousness: gold standard or fool's gold? Prog Brain Res. 2009;177:33–48.
40. Laureys S, Schiff ND. Coma and consciousness: paradigms (re)framed by neuroimaging. NeuroImage. 2012;61(2):478–91.
41. Schnakers C, Majerus S, Goldman S, Boly M, Eeckhout P, Gay S, et al. Cognitive function in the locked-in syndrome. J Neurol. 2008;255(3):323–30.
42. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet. 1974;2(7872):81–4.
43. Giacino JT, Kalmar K, Whyte J. The JFK coma recovery scale-revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil. 2004;85(12):2020–9.
44. Hampshire A, Parkin BL, Cusack R, Espejo DF, Allanson J, Kamau E, et al. Assessing residual reasoning ability in overtly non-communicative patients using fMRI. Neuroimage Clin. 2012;2:174–83.
45. Baddeley AD. A 3 min reasoning test based on grammatical transformation. Psychon Sci. 1968;10(10):341–2.
46. Peterson A, Naci L, Weijer C, Cruse D, Fernández-Espejo D, Graham M, et al. Assessing decision-making capacity in the behaviorally nonresponsive patient with residual covert awareness. AJOB Neurosci. 2013;4(4):3–14.

Chapter 6
Taking Care of Patients with Disorders of Consciousness: Caregivers' Burden and Quality of Life

Matilde Leonardi, Davide Sattin, and Venusia Covelli

This thing has totally changed my life. Now I am talking about it, I can talk about it but unfortunately…, I have not resigned myself to it. I shouldn't say it, but I live in another reality. I'm determined to do like this: when I am with my husband it's a life, but when I leave the long-term care unit, it's another life. I have my grandchildren, I have my children, I have relatives, so I'm never alone. I don't know if it's right or wrong….
(A patient's wife)

Abstract The aim of this contribution is to present the main results of several studies that analyzed the burden of caregivers of patients with disorder of consciousness (DOC) and its impact on caregivers' life. First of all, a distinction between the term "formal" and "informal" caregivers is made, and a presentation of "burden" concept is introduced. Analyzing recent literature available on caregiving and burden of informal caregivers of patients with DOC, the authors found a difficulty in identifying a simple and univocal definition of burden concept. The chapter will then describe the main effects of burden on the life of caregivers of DOC patients, considering a multifaceted burden concept. In particular, the authors will report results on an objective dimension of burden (which include pragmatic changes on personal life, such as economic condition, work activities, hobbies, and daily activities) and a subjective dimension. The latter will be described distinguishing between interpersonal level

M. Leonardi • D. Sattin (✉)
SOSD Neurology, Public Health, Disability—Scientifics Directorate, Neurological Institute IRCCS C.Besta Foundation, Via Celoria 11, Milan, Italy
e-mail: davide.sattin@istituto-besta.it

V. Covelli
Department of Psychology, e-Campus University, Milan, Italy

C. Schnakers, S. Laureys (eds.), *Coma and Disorders of Consciousness*,
DOI 10.1007/978-3-319-55964-3_6

(self-perception in relation to the environment, roles definition, interpersonal relations with the patients, and others) and intrapersonal level (anxiety and depression symptoms, general mental health, prolonged grief disorder, and personal strategies to face a stressful situation). Perspectives of possible future studies and interventions on caregivers' burden will be finally discussed.

Introduction

Vegetative and minimally conscious state diagnoses can be either acute and reversible or chronic and irreversible conditions [1] that often last many years or even decades, posing a significant demand on healthcare systems. Patients with diagnosis of vegetative (VS) and minimally conscious state (MCS) have a severe disability and require a tailored support. In fact, from the perspective of the International Classification of Functioning, Disability and Health (ICF) [2], persons with DOC demonstrate extreme low levels of functioning and require high levels of medical and nursing care for extended periods of time [3, 4]. In particular, patients with DOC are unable to show or show limited behaviors suggestive of cognitive-mediated process. Considering this peculiar feature, it is clear that caregivers have to completely manage the person they care for and that patients are unable to respond verbally to their families or have a very limited communicative code. The purpose of the UN Convention on the Rights of Persons with Disabilities is "to promote, protect and ensure the full and equal enjoyment of all human rights and fundamental freedoms by all persons with disabilities, and to promote respect for their inherent dignity" [5]. It is therefore crucial to study caregivers' reactions in order to support them and "to provide those health services needed by persons with disabilities specifically because of their disabilities […] and services designed to minimize and prevent further disabilities […]" as reported in Article 25 of the UN convention.

The fundamental role of caregivers of patients with DOC is often well known by medical and nursing staff, who view caregivers as playing a key role for the well-being of patients. Moreover, different papers have demonstrated that patients in VS often show a behavioral response to specific stimuli only if presented by their caregivers, e.g., eye movements after a voice call of a relative [6–9]. A recent paper reported that the assessment of patients with DOC made with caregivers could be useful to detect cognitive-mediated behavioral responses that could be underestimated by professionals who test patients occasionally [6]**.** All these data suggest that the relation between caregivers and patients is extremely strong and that caregivers of patients with DOC are a fundamental resource at clinical and social levels.

A number of studies have demonstrated links between chronic stress associated with caregiving activities and indices of poor health, including risk factors for cardiovascular diseases and poorer immune function [10, 11]. A study by Nobel Prize winner Elizabeth H. Blackburn [12] indicated that perceived stress may be either causally or correlationally related to telomere length and that lymphocytes of indi-

viduals with higher levels of reported stress had aged the equivalent of 9–17 additional years, compared to individuals with lower stress. Studies on burden of caregivers, hence, appear fundamental for the society's well-being, also considering that American Psychological Association reported that 65.7 million Americans (or 29% of the US adult population involving 31% of all US households) served as family caregivers for an ill or disabled relative during the past year, according to estimates from the National Alliance for Caregiving [13].

Who Is the Informal Caregiver of a Patient with DOC?

Before starting to describe the characteristics of caregivers of patients with DOC, an essential distinction has to be made in relation to two adjectives usually associated to this term: *formal* and *informal*. The term formal caregiver seems to be universally accepted, especially from an economic perspective: formal caregivers, in fact, are paid for their caring activities. The term *informal caregiving* is still complex to define indeed. Informal caregiving occurs in relationships characterized by affective bonds and generally encompasses greater tasks and responsibilities than normal adult relationship. Goodhead and McDonald [14] define informal caregiving as "caring for a friend, family member or neighbor who, because of sickness, frailty or disability, can't manage everyday living without help or support." As reported by these authors, "It is not usually based on formal agreement or services specifications." More recently, Gould [15] added the concept of "assuming responsibility for the person who needs help." Based on these definitions, the term caregiving appears strictly related to the situation in which caregiving is provided. In fact, the first variable usually reported after the word "caregiver" is about the type of pathology of the care recipient. Therefore, the following sections will report data specifically on caregivers of patients who acquired a severe brain injury and have a diagnosis of vegetative or minimally conscious state.

Sociodemographic Characteristics

A comparison between sociodemographic characteristics reported by available studies on caregivers of patients with DOC is illustrated in Table 6.1 (the list might not be exhaustive). The literature showed that caregivers are mainly women (70.2%), married, employed, and with an average age around 57 years. On the other hand, patients with DOC is mainly a married man with an average age of 54 years old [16]. In fact, the epidemiology of DOC patient has changed in the last decade, from a young person with DOC due to a posttraumatic event to an adult with DOC due to a nontraumatic event [3, 17].

Table 6.1 Sociodemographic characteristics of caregivers (absolute values)

References	Total sample size *N* (female)	Age (mean, SD, or range)[a]	Work status (*N*)	Relationship to patient (*N*)	Education (*N*)
Tresch et al. [62] [b]	33 (23)	61.2 ± 2.3	–	Spouse = 12 Mother = 1 Father = 1 Son/daughter = 16 Sister =2 Niece = 1	–
Chiambretto et al. [40] [b]	16 (10)	51.0 ± 14.8	Employed = 7 Housewife = 4 Retired = 5	Spouse/partner = 4 Mother = 4 Father = 3 Sibling = 1 Son/daughter = 4	Mean education 10.6 years
Chiambretto and Vanoli [21] [b]	30 (18)	61.7 ± 10.63			
Chiambretto et al. [48]	45(29)	56.13 ± 11.7	Employed = 22 Unemployed = 23	Spouse/partner = 17 Parent = 17 Other = 11	Middle school or lower = 16 High school and higher = 29
Leonardi et al. [16]	487 (337)	52.3 ± 13.09	Employed = 239 Unemployed = 10 Housewife = 115 Retired = 118 Other = 5	Spouse/ partner = 195 Son/daughter = 96 Parent = 93 Other = 103	–
Giovannetti et al. [63]	35 (30)	38.7 ± 6.7	White collar = 6 Blue collar = 7 Housewife = 18 Other = 4	Mother = 30 Father = 5	Middle school or lower = 2 High school = 20 Master degree or higher = 13
Guarnerio et al. [64]	40 (31)	58.65 ± 11.88	Retired, unemployed, or housewives = 23 Professionals = 17	Spouse/partner = 16 Parents = 11 Brothers/sisters = 7 Sons/daughters = 2 Other = 4	–
Elvira de la Morena and Cruzado [65]	53 (41)	48.02 ± 15.5	Employed = 27 Unemployed = 6 Housewife = 11 Retired = 5 Other = 4	Spouse/partner = 18 Son/daughter = 15 Parent = 8 Sister/brother = 7 Others = 5	Middle school or lower = 24 High school = 16 Master degree = 13
Cruzado and Elvira de la Morena [53]	53 (41)	48.02 ± 15.54 Range 21–78	Employed = 27 Unemployed = 6 Housewife = 11 Retired = 5 Other = 4	Spouse/partner = 18 Son/daughter = 15 Parent = 8 Sister/brother = 7 Others = 5	Middle school or lower = 24 High school = 16 Master degree = 13
Hamama-Raz [37][b]	12 (12)[c]	61.4 Range 37–83	Employed = 3 Retired = 9	Spouse = 12	13.3 mean education

Table 6.1 (continued)

References	Total sample size *N* (female)	Age (mean, SD, or range)[a]	Work status (*N*)	Relationship to patient (*N*)	Education (*N*)
Covelli et al. [41]	15 (15)[c]	57 (32–78)	–	Spouse/partner = 7 Mother = 8	Middle school or lower = 6 High school = 8 Master degree = 1
Romaniello et al. [55]	19 (15)	55.85 ± 10.91	Employed = 11 Retired = 7 Sick leave = 1	Parent = 1 Son/daughter = 3 Spouse/partner = 15	Middle school or lower = 9 High school = 7 Master degree = 3
Cipoletta et al. [52][b]	24 (19)	Range 32–70	Employed = 14 Unemployed/ retired/ resigned/ = 10	Mother = 6 Father = 1 Spouse = 8 Son/daughter = 7 Sister = 1 Niece = 1	–
Bastianelli et al. [66][b]	52 (30)	Range 19–85	Employed = 18 Housewife = 11 Retired = 19 Student = 1 Not evaluated = 3	Partners = 38.5% Parents = 36.5% Children = 25%	–
Giovannetti et al. [50]	20 (14)	58 ± 10.5	–	–	–
Moretta et al. [18]	24 (15)	47.39 ± 14.86	White-collar = 3 Factory worker = 3 Teacher = 2 Unemployed = 2 Housewife = 9 Retired = 2 Other job = 3	Spouse =10 Parent = 9 Son/daughter = 5	Middle school or lower = 14 High school = 6 Master degree = 4
Corallo et al. [60]	48 (30)	50.19 ± 15.09	–	–	–
Corallo et al. [61]	50 (26)	52.88 ± 11.61	–	Mother = 14 Wife = 8 Daughter = 2 Sister = 2 Son = 8 Husband = 12 Brother = 4	
Giovannetti et al. [20]	129 (88)	52.81 ± 13.05	Employed = 57 Unemployed = 14 Housewife = 16 Retired = 32 Other = 10	Spouse/partner = 61 Son/daughter = 18 Parent = 28 Other = 22	Middle school or lower =60 High school = 48 Degree or higher = 21

(continued)

Table 6.1 (continued)

References	Total sample size *N* (female)	Age (mean, SD, or range)[a]	Work status (*N*)	Relationship to patient (*N*)	Education (*N*)
Gourdarzi et al. [38][b]	13 (10) family cg 3 (1) professional cg	30.77 ± 7.18	–	–	–
Noohi et al. [39][b]	12 (9)	36.3	Housewife = 3	Mother = 4 Father = 2 Son = 2 Brother = 1 Spouse = 1 Professional caregiver = 2	Middle school or lower = 2 High school = 6 Master degree = 4

[a]Mean and SD reported were calculated on available data
[b]Study especially addressed to VS patients
[c]Study especially addressed to female caregivers

What Is the Main Motivation for Caregiving?

Based on a study by Leonardi et al. [16], caregivers take care of their relatives for different reasons. Among them, caregivers reported that they thought they could do it better than everybody else and, secondarily, because there were no other people that could do it or because others had no time available. Similar findings were also reported by Moretta and colleagues [18]. Furthermore, as reported by Huber and Kuehlmeyer [19], *the decision to stay with and care of patients is not a voluntary one* but depends on the type of responsibility in the relationship: asymmetric responsibility between a mother and a son and reciprocal responsibility between partners or friends. This means that a person becomes a caregiver unintentionally or without consciously choosing to be one. The chance of being a caregiver is part of the relationship with the other person (spouse, partner, son, parent, and so on), and the type of reciprocal responsibility may influence the reaction to the experience of caring [19].

Hours of Care and Support for Caring

Caregiving activities are very demanding. Caregivers spend more than 3 h per day with their relatives [16] for 5 days a week. A study on 129 caregivers [20] reported an average of 6 h of care per day; 77.5% did not receive any financial material or personnel support. Focusing on working caregivers of this sample, 75% of the full-time employed and 52.9% of the part-time employed dedicated more than 3 h per day to their relative. A mean care of 8 h per day was also reported by Moretta and colleagues [18] and 14 (58.3%) out of 24 caregivers interviewed declared that they did

not receive any help from social services. In their research, Chiambretto and Vanoli [21] showed that 53.3% of their sample reported that they were alone in taking care of the patient and did not have anyone to take a break from caring. A focus on caregivers of children in VS or MCS is mandatory too: 29 out of the 36 caregivers interviewed in a recent study assist all day (24 h, 77.1% of patients were at home) their children, and only half of the sample receive family support for caring (65.7% had to quit their job after the event).

Burden: Definition and Concepts

Defining caregiver's burden cross-culturally is a complex task according to many researchers. Very often, the term *burden* has been related to *emotional distress*, but the two terms are different. In fact, the etymology of the term *burden* in old English refers to *a load*, *weight*, *charge*, and/or *duty*, whereas the term *distress* refers to a "circumstance that causes anxiety or hardship" or, in Vulgar Latin, **districtia* to "restraint, affliction, narrowness, etc." and is then mainly related to the emotional aspects of caregiving. Additional examples of terminology reported in literature to define caregiver's burden are *caretaker's role fatigue*, *spousal burnout*, and *role engulfment* [22–24]. In spite of differences in terminology, researchers have been trying to define commonalities among the labels.

In the historical development of the term burden, different variables have been linked to this concept. Some authors [25, 26] recognized the importance of separating activities (feeding, bathing, and moving) from emotions and included both aspects in the term burden. Montgomery et al. [27] further delineated the difference between *objective* (activities) and *subjective* (emotions) burden and specified that objective burden was related to the type of task performed, while subjective burden was related to the characteristics of caregiver. In all situations, an imbalance exists between physical and mental resources required to care for the patient and those available within the family unit or community; the term burden seems to be strictly related to this equilibrium. The gradual increase in both physical (objective) and emotional (subjective) demands produces fatigue, stress, limited social contact, individual and group role adjustment, and altered self-esteem. As Zarit, Reever, and Bach-Peterson [28] conclude, *it is the characteristics of the caregiving situation and availability of resources, rather than the condition of the recipient, that has a direct relationship to the caregiver's well-being*. In line with this conceptualization, Garlo [29] observed that burden was associated with perceived needs of support during daily tasks and not with the patient's objective needs for assistance; this suggests that burden may be influenced by adaptation to caregiving role and that interpretation of caregivers' needs may help to plan targeted interventions. George and Gwyther [30] reinforced the definition of caregiver's burden reporting that physical, psychological, or emotional, social, and financial problems were all related to caregiver's burden [27]. They believed that "caregiver's burden" and "caregiver's well-being" were opposite sides of a coin (see also [31, 32]).

As a reader can realize, the term burden seems to have two dimensions (objective and subjective); however, the number of variables that could influence both is difficult to determine. However, a recent review paper, collected data on different assessment scales used to measure burden level in caregivers of cancer patients [33], reported that there were several conceptualizations of burden's dimensions and each tool was developed taking into consideration only variables strictly related to the author's theory underlying the questionnaire. For example, the Caregiving Impact Scale (CIS) developed by Cameron et al. [34] considers different aspects of caregiving, such as employment, active and passive recreation, finances, relationship with partner, self-expression, etc., whereas the Brief Assessment Scale for Caregivers (BASC) [35] evaluates negative and positive personal impact, medical issues, and concern about loved one. Multiple variables influencing the burden concept and, hence, they are difficult to evaluate and impossible to be grouped into a couple of issues, because they represent, and are mediated by, the intrinsic value of human being and the sense of life of each culture to which a person belongs. The fact that the term *burden* is not universally recognized in many *cultures whereas the term caregiving is universal in all cultures is a strong evidence of that*.

For description purposes, in the next pages, we will report the main effects of burden on the life of caregivers of DOC patients, considering a multifaceted burden concept. In particular, we will report results on an *objective dimension of burden* (which includes pragmatic changes in personal life, such as financial conditions, work activities, hobbies, and daily activities) and a *subjective dimension*. The latter will be described by distinguishing between interpersonal level (self-perception in relation to the environment, roles definition, interpersonal relations with the patients, and others) and intrapersonal level (anxiety and depression symptoms, general mental health, prolonged grief disorder, and personal strategies to face a stressful situation).

The Objective Dimension of Burden

Impact on Caregivers' Employment and Economic Status

As stated above, caregivers are mainly employed women, and after the event, one third of them had to quit their job, either permanently or temporarily [16, 18, 20, 36]. A study reported that the family income declared per year was less than 17,000 euros in 40.2% of the 487 caregivers interviewed in a national Italian study [16]. In a previous evaluation, the family income declared per year was between 10,000 and 2000 euros, and financial support was not always provided to the family for all caring expenses. [21]. In a longitudinal evaluation, this trend on employment and economic status tends to be constant [36]: one third of the sample interviewed after 2 years (271 interviewed at T1 out of 487 caregivers interviewed at T0) reported that their economic status worsened after the event and the health condition of the patient was causing family financial difficulties (see also [21, 37]). About worsening of caregivers' economic status, Goudarzi et al. [38] spoke of "family financial erosion"

due to consumable and nonconsumable countless necessities of patients in VS. In fact, family members in most cases become primary "financial supporters" of patients in VS [39], and they support them in almost all healthcare costs.

Impact on Leisure Activities

Caregivers drastically reduced leisure activities. More than 70% out of the 16 caregivers interviewed by Chiambretto and colleagues [40] stated that they led a retired life, having little or no opportunities to cultivate their interests and hobbies or see friends [21]. In particular, in a recent Italian national study [16], 411 out of 487 caregivers declared having reduced leisure activities, above all "meeting friends" (67.7%),"cultivating hobbies or other interests" (50.2%), and "walking or riding a bicycle" (50%) (cfr. Table 6.2); furthermore, 61.1% of them never go to the theater

Table 6.2 Changes in and frequency of attending activities in free time

	Attending friends	Attending venues	Reading books, newspapers	Watching TV or listening to the radio	Walking or riding a bicycle	Cultivating hobbies or other interests	Going to the theatre or to the cinema
Changes in spending free time due to care for the patient (% of caregivers)							
I do it more often than before	15 (3.1%)	9 (1.8%)	62 (12.7%)	51 (10.5%)	22 4.5%)	15 (3.1%)	6 (1.2%)
I do it as often as before	37 (7.6%)	16 (3.3%)	137 (28.1%)	153 (31.4%)	41 (8.4%)	43 (8.8%)	32 (6.6%)
I do it less often than before	330 (67.6%)	232 (47.5%)	167 (34.2%)	213 (43.6%)	244 (50.0%)	245 (50.2%)	183 (37.5%)
I have never done it before	40 (8.2%)	157 (32.2%)	50 (10.2%)	5 (1.0%)	112 (23.0%)	109 (22.3%)	193 (39.5%)
Missing	66 (13.5%)	74 (15.2%)	72 (14.8%)	66 (13.5%)	69 (14.1%)	76 (15.6%)	74 (15.2%)
Frequency of attending the above activities in free time (% of caregivers)							
Always	35 (7.2%)	13 (2.7%)	95 (19.5%)	121 (24.8%)	27 (5.5%)	19 (3.9%)	5 (1.0%)
Often	30 (6.1%)	8 (1.6%)	103 (21.1%)	115 (23.6%)	38 (7.8%)	30 (6.1%)	12 (2.5%)
Sometimes	266 (54.5%)	151 (30.9%)	176 (36.1%)	198 (40.6%)	167 (34.2%)	171 (35.0%)	125 (25.6%)
Never	115 (23.6%)	265 (54.3%)	75 (15.4%)	20 (4.1%)	212 (43.4%)	220 (45.1%)	298 (61.1%)
Missing	42 (8.6%)	51 (10.5%)	39 (8.0%)	34 (7.0%)	44 (9.0%)	48 (9.8%)	48 (9.8%)

Note: Percentage of 487 caregivers interviewed (Leonardi et al. [16])

or to the cinema or see friends or venues (54%). As reported in a qualitative study [41], daily activities and personal interests changed in relation to the place where the patient was hosted (at home versus long-term care), mainly because caregivers of patients in long-term care institutions had more possibilities to take a break from their caring activities, instead of caregivers of patient living at home (who often take care of their family 24 h per day).

The Subjective Dimension of Caregivers' Burden: Individual and Interpersonal Relation Perceptions

The subjective dimension of burden has been extensively studied over the last 20 years. In particular, the following section reports how the prolonged uncertainty in patient's health status (we do not know if or when it will improve or worsen) impacts on caregivers' life perceptions in their interpersonal and intrapersonal levels.

Who Am I? Who Are You? Loss of Identity: A New Role and a New Person

The feeling of losing oneself or a loss of identity is a common perception reported by caregivers. This perception is strictly related to the caregiver's new role that often becomes predominant on others. Caregivers have to negotiate their previous life and the persons they were by adapting to a new reality. If these persons were before primarily wives or mothers, and maybe workers, after the event, they become caregivers above all. Unfortunately, caregivers' role is not explicitly recognized by them, and activities of taking care fall under other roles (i.e., *I am a mother, so I take care of him*) [41], and it was often a result of engulfment in the caregiver's role. Loss of identity and the need to maintain their own sense of self were also described by caregivers of patients with different diagnoses, such as Alzheimer's, Parkinson's, and heart diseases and cancer. On the other hand, for some caregivers, the event has spurred the discovery of a new way of being. In fact, despite the difficult situation, caregivers may discover themselves as being new persons with unknown strength [41]. Some of them had to change in order to manage their difficult situation, and this change is more evident in caregivers who have been taking care of their relatives for more than 2 years [41]. Hamama-Raz et al. [37] described that wives of patients in VS experienced an empowered sense of self-esteem and inner strength related to their love and feelings of responsibility and commitment to their husband. At the same time, they reported a sense of isolation, emotional grief, reduction of hope, and feelings of mourning.

You Are. You Were

Caregivers' perception about DOC patients also change; in particular, it is like the relative is another person with whom caregivers shared their past [41, 42]. Other studies on caregivers of terminally ill or chronically ill patients revealed that due to the changes related to the relatives' health condition, stroke patients no longer seemed the same persons that the caregiver had known. Furthermore, especially for woman caregivers, they change the way in which they usually see and describe the patient. For example, as authors reported, caregivers describe the relative as another child or a grown up child, but not as an adult, and this is might related to the patients' health condition requiring constant assistance for doing everything [19]. So it changes also the relationship with the patient and the way that caregiver talks to their relative. As Cipolletta and colleagues noted [43], the communication between caregivers and patients is nonverbal, and close relationship between them is maintained throughout physical contacts [20].

Interpersonal Relations and Social Support

The event had an impact on the caregivers' informal social networks of friends or relatives. On the other hand, the attendance of new environment (i.e., hospital or long-term institute) had the opportunities to caregivers to establish new interpersonal relationships. Caregivers of patients at home established new relationships too, for example, with healthcare professionals coming daily or weekly to take care of the relative [41]. As recently reported in their qualitative study, Noohi and colleagues [39] stated that "receiving social support is the primary concern" of caregivers and "delivering care, without receiving information, advice and education, counselling and emotional, financial and practical support is extremely painful for family caregivers."

The Intrapersonal Dimension of Burden: Psychological Aspect and Personal Strategies to Face a Situation

Concerning the intrapersonal dimension correlated to burden, in the next section, authors present results on two different aspect: in the first one are reported data related to pathological aspect of emotional status of caregivers, whereas in the second one are reported results on personal strategies to face a problem or a situation.

Quantitative Assessment and Clinical Evaluation of Emotional Distress

DOC caregivers' emotional distress was evaluated in several studies using different quantitative assessment scales in the last years, in order to analyze if caregivers presented symptoms that could be classified as "pathological" as compared to normative or control samples. Anxiety and depression symptoms in caregivers have been broadly investigated in the literature, but results in relation to symptoms and caregivers' gender are still debated. In Table 6.3 were reported results of several studies on this last issue, and almost all papers, using different assessment tools to evaluate anxiety and depression symptoms, reported high levels of emotional distress in caregivers of patients with DOC.

Table 6.3 Assessment scale used to evaluate emotional distress

References	Assessment scale used to assess anxiety symptoms	Reported results	Assessment scale used to assess depression symptoms	Reported results	Did article report data on differences related to caregiver gender?	Time from acute event (mean, SD and/or range)
Chiambretto and Vanoli [21][a]	CBA 2.0 STAI-X	Both male and female caregivers showed more state and trait anxiety symptoms than normative sample	CBA2.0	Both male and female caregivers showed more depressive symptoms than normative sample	Yes	52.93 ± 42.33 (range 2–132) months
Chiambretto et al. [48] [a]	CBA 2.0	Scores of male caregivers were significantly higher than the Italian reference norms for state anxiety	FSQ2 CBA 2.0	Scores of male caregivers were significantly higher than the Italian reference norms for depressive symptoms	Yes	22.6 t20.3 (range 4–78) months
Leonardi et al. [16]	STAI-Y	High level of tension and apprehension compared to the average of the Italian normative sample	BDI-II	59.4% somatic affective score > 95 percentile78.5% cognitive score > 95 percentile	Yes	mean (SD; min–max) 4.0 (3.6; 0.1–23.4)
Giovannetti et al. [63]	STAI-Y	Caregivers reported higher level of state anxiety and trait anxiety	BDI-II	57.2% of caregivers exceeded the threshold of 85 percentile and reported at least mild depressive symptoms	No	mean (SD; min–max) 4.0 (3.6; 0.1–23.4)

Table 6.3 (continued)

References	Assessment scale used to assess anxiety symptoms	Reported results	Assessment scale used to assess depression symptoms	Reported results	Did article report data on differences related to caregiver gender?	Time from acute event (mean, SD and/or range)
Giovannetti et al. [50]	STAI-Y	Caregivers of post-acute patients reported higher state of anxiety than caregivers of long-term patients	BDI-II	More than 60% of the sample showed at least mild depressive symptoms, of whom more than30% were allocated in the severe range	No	<1 year: vs. 111 (32.6) month, mcs 31 (21.1); 1–2 years: vs. 57 (16.8) months, mcs 90 (61.2); 3–5 years: vs. 96 (28.2), mcs 9 (6.1); >5 years: vs. 76 (22.4), mcs 17 (11.6)
Pagani et al. [67]	STAI-Y	Both male and female state and anxiety had a significant negative relationship with mental health; women reported significantly higher scores in both state and trait anxiety	BDI-II	Female: BDI-II scores had a significant negative relationship with mental health; women reported significantly higher scores as well as in BDI-II scores	Yes	Male caregivers 3.10 (3.24) years; female caregivers 3.72 (3.65) years
Pagani et al. [68]	STAI-Y	Greater anxiety symptoms were significantly associated to greater needs expressed	BDI-II	Greater depressive symptoms were significantly associated with greater perceived burden which was positively associated to needs expressed	Yes	Mean patients disease duration: 3.4 years (sd 3.3)
Guarnerio et al. [64]			QD	10 (25%) caregivers showed scores above threshold	No	52.18 months (sd 44.51; range: 7–186)
Elvira de la morena and Cruzado [65]	BAI	28.30% of caregivers showed anxiety (cutoff ≥ 21)	BDI	30.20% of caregivers showed depression symptoms	No	Mean 38.63 months (sd 37.54, range 27.07–50.18)

(continued)

Table 6.3 (continued)

References	Assessment scale used to assess anxiety symptoms	Reported results	Assessment scale used to assess depression symptoms	Reported results	Did article report data on differences related to caregiver gender?	Time from acute event (mean, SD and/or range)
Covelli et al. [36]	–	–	BDI-II	Somatic-affective score and total score decrease over time	No	Time between acute event and T0 (in years) mean(SD; min–max) 4.0 (3.6; 0.1–23.4) Time between acute event and T1 (in years) mean (SD; min–max) 6.7 (3.6; 1.8–26.1)
Bastianelli et al. [66][a]	AD	51.92%of caregivers reported normal scores of anxiety	AD	59.62% of the sample has shown normal value of depression in ad scales	Yes	Most caregivers (50%) cared for their patients for 1–6 years, with 26.9 percent for less than 1 year and 23.1 percent for more than 6 years
Cipolletta et al. [52][a]	AD	37.7% of caregivers posted clinical relevant scores of anxiety and depression	AD		Yes	Most caregivers (57.5%) had cared for their patients for 1–6 years, with 20% for less than 1 year and 22.5% for more than 6 years
Moretta et al. [18]	STAI-Y	High level of anxiety in 12 caregivers(66.7%; five subjects scored above the 90 centile of the normative data); association between state anxiety inventory score with the Caregiver Needs Assessment total score and with the subscale "need of social/emotional support"	BDI-II	Presence of depressive symptoms (score > 13) in 15/18 caregivers(83.3% of the sample at the follow-up; two had mild symptoms, nine moderate, four severe) higher scores on Beck depression inventory-II in caregivers with prolonged grief disorder; positive association with the Family Strain Questionnaire subscale "emotional burden"	No	Brain injury at a mean of 9.8 months (range 2–50)

Table 6.3 (continued)

References	Assessment scale used to assess anxiety symptoms	Reported results	Assessment scale used to assess depression symptoms	Reported results	Did article report data on differences related to caregiver gender?	Time from acute event (mean, SD and/or range)
Corallo et al. [60]	STAI-Y		BDI-II		No	
Corallo et al. [61]	SCL 90	Caregivers have shown higher level of psychological distress	SCL 90		No	–
Giovannetti et al. [20]	STAI-Y	Male (<50 years old): state and trait anxiety were higher than normative sample Female(>50to): state anxiety higher than normative sample	BDI-II	BDI-II score was not correlated to time dedicated to care	Yes	40 months

AD Anxiety and Depression Short Scale, *BAI* Beck anxiety inventory, *BDI-II* Beck depression inventory-II, *CBA 2.0* cognitive behavioral assessment 2.0, *FSQ* Family Strain Questionnaire, *QD* Depression Questionnaire, *SCL 90* Symptom Checklist-90, *STAI-Y* state-trait anxiety inventory-form Y, *STAI-X* state-trait anxiety inventory-form X

[a]Study especially addressed to SV patients

Ambiguous Loss and Prolonged Grief Disorder

The traumatic event forces caregiver to experience a loss as regards to what the patient was in the past. More precisely, their relative is psychically and psychologically present *in a different manner respect to the past*. This condition called "*ambiguous loss*" [42] was previously defined by Stern in 1988 like an *emotional paradox* for caregivers [44] because it does not allow them to elaborate a strategy of mourning because the patients are not dead.

With regard to the experience of loss and mourning dimension related to the uncertainty patients' clinical conditions, authors refer to different concepts, like *grief* and *anticipatory grief* [45–47]; some studies describe that caregivers of patients with DOC experience a *pathological reaction* described by the *prolonged grief disorder* (PGD) [16, 48], a condition in which one feels imprisoned in memories, regret, and sense of guilt, as a consequence of a loved one's health condition. Studies reported that a range from 15 to 60% of caregivers sample met the prolonged grief disorder (Table 6.4) and that tailored treatments should be developed to help caregivers to care for their relatives without feeling immobilize in a mental state.

Table 6.4 Percentage of caregivers that met the prolonged grief disorder

References	Total sample size *N* (female)	Age (mean, SD or range)[a]	% of sample that met the PG disorder(% female)
Chiambretto et al. [48]	45 (29)	56.13 ± 11.7	35.5 (81.5%)
Leonardi et al. [16]	487 (337)	52.3 ± 13.09	27.58% (n.s.)
Guarnerio et al. [64]	40 (31)	58.65 ± 11.88	15% (n.s.)
Elvira de la Morena and Cruzado [65]	53 (41)	48.02 ± 15.5	60.40% (n.s.)
Cipoletta et al. [43][a]	24 (19)	Range 32–70	37.7% (69.7%)
Bastianelli et al. [66][a]	52 (30)	Range 19–85	38.5% (55%)
Moretta et al. [18]	24 (15)	47.39 ± 14.86	32% (n.s.)
Corallo et al. [60]	48 (30)	50.19 ± 15.09	n.s.

[a]Study especially addressed to VS patients; *n.s.* not specified

Burden and Emotional Distress

The relation between general level of burden and emotional distress was also confirmed by several studies that used the Family Strain Questionnaire (FSQ) (a brief semi-structured interview designed to assess perceived caregiving-related problems that investigated five areas: emotional burden, problems of social involvement, need for knowledge, quality of family relationships, and thoughts of death) [49]. Some authors shown as emotional burden low score were often associated to a strong desire for knowledge about relatives' condition and problems in social involvement [16]. A qualitative analysis of FSQ reported by Chiambretto et al. [48] also showed that 50% of the caregivers declared that they were not in a position to organize caregiving "shifts," that the spiritual dimension seems to be of help to 50% of the subjects, and that more than 70% declared that they led a retired life with little or no opportunity of seeing friends. Giovannetti et al. [50] suggested that caregivers' mental health condition is subject to subtle improvement, that satisfaction with family relationships does not change significantly, and that physical condition tends to deteriorate over time.

Personal Features and Strategies to Face a Stressful Situation

Another aspect related to emotional distress concerns the type of *coping strategies* adopted by a person to cope with stressful situations. Chiambretto et al. [40] found that gender does not influence coping and that both males and females prevalently use coping strategies oriented toward the situation and there was no significant difference between them in the use of coping strategies in long-term care setting. Caregivers of patients hosted in post-acute facilities reported significantly higher scores in Coping Orientation to Problem Experience (COPE) social support and

problem-oriented scales [51], whereas caregivers of VS patients scored significantly higher in avoidance scales compared to caregivers of patients in MCS [16]. Cipolletta et al. [52], instead, reported lower scores in avoidance and problem-oriented scales of COPE in their sample with respect to data presented in Giovannetti et al. [50] but higher scores in religion subscale. Correct or incorrect coping strategies do not exist per definition, but the crucial issue is how coping correlates with emotional state of caregivers; this point needs more investigation in the future.

Coping strategies alone, particularly positive attitude, seem to be significant predictors of the following WHOQOL-BREF domains: psychological health, social relationships, and environment [20]. Cruzado and Elvira del la Morena [53] reported that "acceptance" predicted the absence of depression and anxiety, whereas "denial" was associated with them. Moreover, "self-blame" was associated with depression, and "emotion-focused coping" was associated with high level of anxiety and depression in caregivers of patients with DOC too.

Another issue related to caregivers' reactions to a traumatic situation is the presence of *hopelessness*. Hope is considered an important factor for adapting during suffering [54], and its presence is useful to counterbalance stress and to appraise caregiving experience more positively. Romaniello et al. [55] found that hopelessness may be an important determinant of overall burden in caregivers of patients with DOC, and so authors highlighted the importance of assessing its presence.

Finally, data on another personal feature refers to the *attachment style of caregiver*. In fact, in Romaniello's paper, caregivers with anxious attachment have shown a heightened perception of partner pain [55], and this has some consequences in interpersonal relations such as over solicit professional operators about several aspects, for instance, posture, drugs, or daily hygiene or interacting with strangers; taken together, the features of caregivers with anxious attachment style and hopelessness may contribute to several aspects of total emotional distress and burden perceived.

The Impact on Caregivers' Quality of Life

There is considerable agreement among experts that quality of life can be defined as "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" [56, 57]. Some studies tried to investigate caregivers' perception of their quality of life during care of patients with DOC using the WHOQOL-BREF [57] (a self-administered questionnaire aimed at evaluating QoL measuring the following domains: physical health, psychological health, social relationships, and environment). Giovannetti et al. [20] found that caregivers' scores were significantly lower compared to that of the Italian normative sample for three of four factors, namely, psychological health, social relationships, and environment.

In another article, wrote by the same authors, results in Short-Form 12 Health Survey [58] (a questionnaire used to describe caregiver's health conditions, composed by two factors accounting for "physical component summary" and "mental component summary") suggested that caregivers' mental health condition is subject to subtle improvement, that satisfaction with family relationships does not change significantly over time, and that physical condition tends to deteriorate. This result was also confirmed by Covelli et al. [18]. All these data seem to suggest that caregivers increase their psychological health over time but that their physical level is prone to wear and so they have to change their perception of quality of life over time changing the value system in which they live.

Concluding Remark: The Importance of Support and Targeted Interventions

The definition of guidelines for interventions aimed to support caregivers of patients with DOC is really hard, due to the fact that caregivers are very busy in caring for their relative and the time for their selves, and hence their needs, is relatively short [42]. In fact, the results of quantitative and qualitative studies highlighted that caregivers expressed needs not for themselves but for the patient. More than 75% of 487 caregivers interviewed in the Italian national study [16] reported perceived needs mainly belonging to the factor "information and communication" of the Caregiver Needs Assessment (CNA) (e.g., they need to be informed by physicians and health professionals about what is done to the relative) [59]. In fact, caregivers interviewed by Goudarzi and colleagues [38] expressed that because of the patients' incapacities, they need high levels of care.

In two qualitative studies [41, 42] when invited to express specific needs for themselves, caregivers identified emotional needs (i.e., psychological support, close relationships), needs for space and time for themselves and needs for simplified pathways of care, in the management of relative's health condition [41].

Regarding psychological supports, a previous longitudinal study on caregivers of VS patients highlighted how levels of anxiety, depression, and emotional burnout are slightly better for caregivers who take part in mutual help groups where they can share their own personal experiences [21]. Most recently, the study of Corallo and colleagues [60, 61] confirms that psychological support to families of patients with DOC improves their ability to process the experience of the patient's illness, with no differences between the diagnosis (VS versus MCS). A recent longitudinal study on 216 caregivers of DOC patients provides some preliminary evidences that interventions on caregivers could be useful to reduce the use of some coping strategies (e.g., avoidance) and provides some evidence of how these may help caregivers to improve their condition and reduce the burden. Therefore, more additional efforts are needed on investigating the role of psychological support in large sample of caregivers, so to better design targeted interventions to promote and improve their health and quality of life.

References

1. Bernat JL. Chronic disorders of consciousness. Lancet. 2006;367(9517):1181–92. S0140-6736(06)68508-5 [pii]
2. World Health Organization. The international classification of functioning, disability, and health. Geneva, Switzerland: ICF; 2001.
3. Leonardi M, Sattin D, Raggi A. An Italian population study on 600 persons in vegetative state and minimally conscious state. Brain Inj. 2013;27(4):473–84. doi:10.3109/02699052.2012.750758.
4. Willems M, Sattin D, Vingerhoets AJ, et al. Longitudinal changes in functioning and disability in patients with disorders of consciousness: the importance of environmental factors. Int J Environ Res Public Health. 2015;12(4):3707–30. doi:10.3390/ijerph120403707.
5. United Nations. Convention on the rights of persons with disabilities. 2006. Accessed 4 Jan 2016.
6. Sattin D, Giovannetti AM, Ciaraffa F, et al. Assessment of patients with disorder of consciousness: do different Coma Recovery Scale scoring correlate with different settings? J Neurol. 2014;261(12):2378–86. doi:10.1007/s00415-014-7478-5.
7. Magee WL. Music therapy with patients in low awareness states: approaches to assessment and treatment in multidisciplinary care. Neuropsychol Rehabil. 2005;15(3–4):522–36. doi:10.1080/09602010443000461.
8. Magee WL. Music as a diagnostic tool in low awareness states: considering limbic responses. Brain Inj. 2007;21(6):593–9. 779663591 [pii]
9. Zhu J, Wu X, Gao L, et al. Cortical activity after emotional visual stimulation in minimally conscious state patients. J Neurotrauma. 2009;26(5):677–88. doi:10.1089/neu.2008.0691.
10. McEwen BS. Protective and damaging effects of stress mediators. N Engl J Med. 1998;338(3):171–9. doi:10.1056/NEJM199801153380307.
11. Segerstrom SC, Miller GE. Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry. Psychol Bull. 2004;130(4):601–30. doi:10.1037/0033-2909.130.4.601.
12. Epel ES, Blackburn EH, Lin J, et al. Accelerated telomere shortening in response to life stress. Proc Natl Acad Sci U S A. 2004;101(49):17312–5. 0407162101 [pii]
13. America Psychological Association. Who are family caregivers? 2016. Accessed 4 Jan 2016.
14. Goodhead A, Mcdonald J. Informal caregivers literature review: a report prepared for the National Health Committee. 2007. Accessed 4 Jan 2016.
15. Gould D. Family caregivers and the health care system. In: Levine C, Murray TH, editors. The cultures of caregiving: conflict and common ground among families, health professionals, and policy makers. Baltimore: The John Hopkins Univerisity Press; 2004. p. 5–34.
16. Leonardi M, Giovannetti AM, Pagani M, et al. Burden and needs of 487 caregivers of patients in vegetative state and in minimally conscious state: results from a national study. Brain Inj. 2012;26(10):1201–10. doi:10.3109/02699052.2012.667589.
17. Avesani R, Roncari L, Khansefid M, et al. The Italian National Registry of severe acquired brain injury: epidemiological, clinical and functional data of 1469 patients. Eur J Phys Rehabil Med. 2013;49(5):611–8. R02132981 [pii]
18. Moretta P, Estraneo A, De Lucia L, et al. A study of the psychological distress in family caregivers of patients with prolonged disorders of consciousness during in-hospital rehabilitation. Clin Rehabil. 2014;28(7):717–25. 0269215514521826 [pii]
19. Huber B, Kuehlmeyer K. Perspectives of family caregivers on the vegetative state. In: Jox RJ, Kuehlmeyer K, Marckmann G, et al., editors. Vegetative state—a paradigmatic problem of modern societies: medical, ethical, legal and social perspectives on chronic disorders of consciousness. Berlin Germany: LIT; 2012. p. 97–109.
20. Giovannetti AM, Covelli V, Sattin D, et al. Caregivers of patients with disorder of consciousness: burden, quality of life and social support. Acta Neurol Scand. 2015;132(4):259–69. doi:10.1111/ane.12392.

21. Chiambretto P, Vanoli D. Family reactions to the vegetative state: a follow-up after 5 years. G Ital Med LavErgon. 2006;28(1 Suppl 1):15–21.
22. Ekberg JY, Griffith N, Foxall MJ. Spouse burnout syndrome. J Adv Nurs. 1986;11(2):161–5.
23. Goldstein V, Regnery G, Wellin E. Caretaker role fatigue. Nurs Outlook. 1981;29(1):24–30.
24. Skaff MM, Pearlin LI. Caregiving: role engulfment and the loss of self. Gerontologist. 1992;32(5):656–64.
25. Hoenig J, Hamilton MW. The schizophrenic patient in the community and his effect on the household. Int J Soc Psychiatry. 1966;12(3):165–76.
26. Platt S, Hirsch S. The effects of brief hospitalization upon the psychiatric patient's household. Acta Psychiatr Scand. 1981;64(3):199–216.
27. Montgomery RJV, Gonyea JG, Hooyman NR. Caregiving and the experience of subjective and objective burden. Fam Relat. 1985;34(1):19–26.
28. Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. Gerontologist. 1980;20(6):649–55.
29. Garlo K, O'Leary J, Van Ness P, et al. Burden in caregivers of older adults with advanced illness. J Am Geriatr Soc. 2010;58(12):2315–22. doi:10.1111/j.1532-5415.2010.03177.x.
30. George LK, Gwyther LP. Caregiver well-being: a multidimensional examination of family caregivers of demented adults. Gerontologist. 1986;26(3):253–9.
31. Anderson CS, Linto J, Stewart-Wynne EG. A population-based assessment of the impact and burden of caregiving for long-term stroke survivors. Stroke. 1995;26(5):843–9.
32. Yamamoto-Mitani N, Aneshensel CS, Levy-Storms L. Patterns of family visiting with institutionalized elders: the case of dementia. J Gerontol B Psychol Sci Soc Sci. 2002;57(4):S234–46.
33. Tanco K, Park JC, Cerana A, et al. A systematic review of instruments assessing dimensions of distress among caregivers of adult and pediatric cancer patients. Palliative Supportive Care. 2016;29:1–15.
34. Cameron JI, Franche RL, Cheung AM, et al. Lifestyle interference and emotional distress in family caregivers of advanced cancer patients. Cancer. 2002;94(2):521–7. doi:10.1002/cncr.10212.
35. Gwyther LP, George LK. Caregivers for dementia patients: complex determinants of well-being and burden. Gerontologist. 1986;26(3):245–7.
36. Covelli V, Sattin D, Giovannetti AM, et al. Caregiver's burden in disorders of consciousness: a longitudinal study. Acta Neurol Scand. 2016; doi:10.1111/ane.12550.
37. Hamama-Raz Y, Zabari Y, Buchbinder E. From hope to despair, and back: being the wife of a patient in a persistent vegetative state. Qual Health Res. 2013;23(2):231–40. doi:10.1177/1049732312467537.
38. Goudarzi F, Abedi H, Zarea K, et al. Multiple victims: the result of caring patients in vegetative state. Iran Red Crescent Med J. 2015;17(6):e23571. doi:10.5812/ircmj.23571.
39. Noohi E, Peyrovi H, ImaniGoghary Z, et al. Perception of social support among family caregivers of vegetative patients: a qualitative study. Conscious Cogn. 2016;41:150–8. doi:10.1016/j.concog.2016.02.015.
40. Chiambretto P, Rossi Ferrario S, Zotti AM. Patients in a persistent vegetative state: caregiver attitudes and reactions. Acta Neurol Scand. 2001;104(6):364–8. 107 [pii]
41. Covelli V, Cerniauskaite M, Leonardi M, et al. A qualitative study on perceptions of changes reported by caregivers of patients in vegetative state and minimally conscious state: the "time gap experience". Scientific World J. 2014;2014:657321. doi:10.1155/2014/657321.
42. Giovannetti AM, Cerniauskaite M, Leonardi M, et al. Informal caregivers of patients with disorders of consciousness: experience of ambiguous loss. Brain Inj. 2015;29(4):473–80. doi:10.3109/02699052.2014.990514.
43. Cipolletta S, Pasi M, Avesani R. Vita tua, mors mea: the experience of family caregivers of patients in a vegetative state. J Health Psychol. 2014;21(7):1197–206. 1359105314550348 [pii]

44. Stern JM, Sazbon L, Becker E, et al. Severe behavioural disturbance in families of patients with prolonged coma. Brain Inj. 1988;2(3):259–62.
45. Rando T. Grief, dying and death: clinical interventions for the caregiver. Champaign: Research Press; 1984.
46. Rando T. Loss and anticipatory grief. Lexington: Lexington Books; 1986.
47. Rando T. Clinical dimensions of anticipatory mourning: theory and practice in working with the dying, their loved ones, and their caregivers. Champaign: Research Press; 2000.
48. Chiambretto P, Moroni L, Guarnerio C, et al. Prolonged grief and depression in caregivers of patients in vegetative state. Brain Inj. 2010;24(4):581–8. doi:10.3109/02699051003610490.
49. Rossi Ferrario S, Baiardi P, Zotti AM. Assessment of problems associated with caregiving: the family strain questionnaire. G Ital Med Lav Ergon. 2001;23(1):25–9.
50. Giovannetti AM, Leonardi M, Pagani M, et al. Burden of caregivers of patients in vegetative state and minimally conscious state. Acta Neurol Scand. 2013;127(1):10–8. doi:10.1111/j.1600-0404.2012.01666.x.
51. Carver CS, Scheier MF, Weintraub JK. Assessing coping strategies: a theoretically based approach. J Pers Soc Psychol. 1989;56(2):267–83.
52. Cipolletta S, Gius E, Bastianelli A. How the burden of caring for a patient in a vegetative state changes in relation to different coping strategies. Brain Inj. 2014;28(1):92–6. doi:10.3109/02699052.2013.857789.
53. Cruzado JA, Elvira de la Morena MJ. Coping and distress in caregivers of patients with disorders of consciousness. Brain Inj. 2013;27(7–8):793–8. doi:10.3109/02699052.2013.793402.
54. Utne I, Miaskowski C, Paul S, et al. Association between hope and burden reported by family caregivers of patients with advanced cancer. Support Care Cancer. 2013;21(9):2527–35. doi:10.1007/s00520-013-1824-5.
55. Romaniello C, Farinelli M, Matera N, et al. Anxious attachment style and hopelessness as predictors of burden in caregivers of patients with disorders of consciousness: a pilot study. Brain Inj. 2015;29(4):466–72. doi:10.3109/02699052.2014.989402.
56. The World Health Organization. The World Health Organization quality of life assessment (WHOQOL): position paper from the World Health Organization. Soc Sci Med. 1995;41(10):1403–9. doi:10.1016/0277-9536(95)00112-K.
57. Szabo S, Orley J, Saxena S, et al. An approach to response scale development for cross-cultural questionnaires. Eur Psychol. 1997;2:3270–6.
58. Ware J, Kosinski M, Keller S. SF-12: how to score the SF-12 physical and mental health summary scales. Boston: The Health Institute, New England Medical Centre; 1995.
59. Moroni L, Sguazzin C, Filipponi L, et al. Caregiver Need Assessment: a questionnaire for caregiver demand. G Ital Med Lav Ergon. 2008;30(3 Suppl B):B84–90.
60. Corallo F, Bonanno L, De Salvo S, et al. Effects of counseling on psychological measures in caregivers of patients with disorders of consciousness. Am J Health Behav. 2015;39(6):772–8. doi:10.5993/AJHB.39.6.4.
61. Corallo F, Bonanno L, Lo Buono V, et al. Psychological distress of family members of vegetative and minimally conscious state patients. Acta Medica Mediterranea. 2015;31:297.
62. Tresch DD, Sims FH, Duthie Jr EH, et al. Patients in a persistent vegetative state attitudes and reactions of family members. J Am Geriatr Soc. 1991;39(1):17–21.
63. Giovannetti AM, Pagani M, Sattin D, et al. Children in vegetative state and minimally conscious state: patients' condition and caregivers' burden. Scientific World J. 2012;2012:232149. doi:10.1100/2012/232149.
64. Guarnerio C, Prunas A, Della Fontana I, et al. Prevalence and comorbidity of prolonged grief disorder in a sample of caregivers of patients in a vegetative state. Psychiatr Q. 2012;83(1):65–73. doi:10.1007/s11126–011–9183-1.
65. Elvira de la Morena MJ, Cruzado JA. Caregivers of patients with disorders of consciousness: coping and prolonged grief. Acta Neurol Scand. 2013;127(6):413–8. doi:10.1111/ane.12061.

66. Bastianelli A, Gius E, Cipolletta S. Changes over time in the quality of life, prolonged grief and family strain of family caregivers of patients in vegetative state: A pilot study. J Health Psychol. 2014;21(5):844–52. pii:1359105314539533
67. Pagani M, Giovannetti AM, Covelli V, et al. Physical and mental health, anxiety and depressive symptoms in caregivers of patients in vegetative state and minimally conscious state. Clin Psychol Psychother. 2014;21(5):420–6. doi:10.1002/cpp.1848.
68. Pagani M, Giovannetti AM, Covelli V, et al. Caregiving for patients in vegetative and minimally conscious states: perceived burden as a mediator in caregivers' expression of needs and symptoms of depression and anxiety. J Clin Psychol Med Settings. 2014;21(3):214–22. doi:10.1007/s10880–014-9399-y.

Chapter 7
How Does Spasticity Affect Patients with Disorders of Consciousness?

Géraldine Martens, Marguerite Foidart-Dessalle, Steven Laureys, and Aurore Thibaut

Abstract Spasticity is a frequent issue encountered by brain-damaged patients, arising from an anarchic reorganization of the central nervous system that may significantly alter motor function. While it is well described in patients with a lesion of the descending corticospinal system, little is known about the occurrence and physiopathology of this disorder in patients with more complex brain lesions and disorders of consciousness (coma, unresponsive wakefulness syndrome, and minimally conscious state). Most of the time, these patients are bedridden and lack voluntary motor command which favors spasticity to occur and may lead to complications including pain, loss in range of motion, or bed sores. Given the inability for many of these patients to express their pain or discomfort and knowing that spastic syndromes may restrain them to express signs of consciousness, the multimodal treatment of this spasticity is crucial for their management. In the present chapter, we describe the physiopathology and the current available treatments of spasticity in this specific population of severe brain-injured patients with disorders of consciousness.

G. Martens, M.Sc • S. Laureys, M.D., Ph.D.
Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium

M. Foidart-Dessalle, M.D.
Department of Physical Medicine and Rehabilitation, University Hospital of Liege, Liege, Belgium

A. Thibaut, Ph.D. (✉)
Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium

Neuromodulation Center, Spaulding Rehabilitation Hospital, Harvard Medical School, 79/96 13th avenue, 02129 Charlestown, MA, USA
e-mail: athibaut@ulg.ac.be

C. Schnakers, S. Laureys (eds.), *Coma and Disorders of Consciousness*,
DOI 10.1007/978-3-319-55964-3_7

List of Abbreviations

CNS	Central nervous system
DOC	Disorders of consciousness
EMG	Electromyogram
MAS	Modified Ashworth Scale
MCS	Minimally conscious state
MTS	Modified Tardieu Scale
ROM	Range of motion
TBI	Traumatic brain injury
UMN	Upper motor neuron
UWS	Unresponsive wakefulness syndrome

Introduction

Spasticity is a motor disorder occurring after a lesion of the central nervous system (CNS) such as stroke, spinal cord injury, multiple sclerosis, or traumatic brain injury [1]. This trouble is commonly defined as *a motor disorder, characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex as one component of the upper motor neuron (UMN) syndrome* [2]. The UMN syndrome classically shows positive (e.g., increased tendon reflexes, clonus, positive Babinski sign) and negative signs (e.g., muscle weakness, loss of dexterity, fatigability) [3]. A more recent definition describes spasticity as *a disordered sensori-motor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles* [3]. Actually, there are many and various definitions of spasticity [4, 5] which shows there is no any consensus yet on its specific meaning. Nonetheless, notions of increased hypertonia and hyperreflexia are widely accepted through the different definitions of spasticity [1, 6, 7]. However, a specific definition of spasticity accepted by all still remains to be determined.

This disorder occurs in about one-third of patients who suffered from a stroke [8] or a traumatic brain injury (TBI) [9] and can reach up to 89% in chronic patients with disorders of consciousness (DOC) [10]. These altered states of consciousness include coma, unresponsive wakefulness syndrome (UWS), and minimally conscious state (MCS). While coma is characterized by the complete loss of both wakefulness and awareness [11], the UWS means that the patient has recovered sleep-wake cycles but without any sign of awareness of self, nor the environment [12, 13]. A patient in MCS shows inconsistent but clearly discernible behavioral signs of consciousness (e.g., response to command, visual pursuit, object manipulation, or verbalization) [14]. However, he/she is unable to functionally communicate yet.

Only a few studies have investigated spasticity and its side effects or consequences in patients with DOC, whereas these patients often raise serious issues

about their daily therapeutic management. Therefore, it is of a high importance to take care of this disorder in this population of noncommunicative brain-injured patients.

Clinically, spasticity is demonstrated through exaggerated tendon tap reflexes associated with an increased and velocity-related resistance of a muscle when passively stretched [15]. Yet, patients suffering from spasticity may also present, in addition to hyperexcitability of the stretch reflex, spastic dystonia (muscle constriction at rest) or spastic cocontractions (contraction of both agonist and antagonist muscles during the volitional movement) [10]. Spasticity arises from a dissociation of sensory input (e.g., passive movement) from the motor responses, resulting in hyperexcitability of these latter by increased segmental CNS processing [16, 17]. In chronic paralyzed patients, spasticity is often associated with ankylosis of the joints, or even joint fixation. In this case, the velocity-related resistance of a muscle when passively stretched is more difficult to assess.

Spasticity has to be objectively assessed, in order to follow its evolution over time. To this end, several scales have been developed and validated [18]. The most commonly used are the Modified Ashworth Scale (MAS) and the Modified Tardieu Scale (MTS) (Table 7.1). The MAS measures the level of resistance to a passive movement. This scale is widely used in both research and clinical practice since it is fast and easy to use, but validation studies showed "poor" to "moderate" inter-rater reliability despite a "moderate" to "good" intra-rater reliability [19, 20]. The investigator assessing spasticity should thus always be the same person.

The MAS does not take into account the influence of the velocity of the passive movement, whereas its importance is specified in several definitions. On the other hand, the MTS does take into account this parameter using three different velocities (low, normal, and fast), and it includes the angle of contraction outbreak as well. However, its validity still needs to be proven [21].

Other clinical tools are used to quantify spasticity in a more objective way. For instance, electromyography (EMG) is a commonly used neurophysiological method assessing muscles' response to mechanical or electrical stimuli. The electrical signals preceding mechanical muscle activity can provide information about muscle properties and neuromuscular control. Therefore, neurophysiological assessments are often employed to investigate the effects of therapeutic interventions on spasticity, as well as to understand the different pathways involved [22]. Biomechanical standardized methods involving isokinetic dynamometers are other options to evaluate spasticity in an objective manner [23, 24]. An "optimal" evaluation would reside in a combination of electrophysiological and biomechanical techniques to see if the mechanical response of the muscle is proportional to the electrical signal. Indeed, while the EMG measurement only allows determining the stretch reflex threshold, adding a biomechanical assessment would permit evaluating the relationship between stretch velocity and the evoked stretch reflex-mediated torque generated from the stretched muscle [25]. Assessing patient's spasticity using reliable and sensitive tools is crucial in order to develop and adjust patients' most effective antispastic treatment.

Table 7.1 The Modified Ashworth Scale (MAS) and the Modified Tardieu Scale (MTS) [10]

Modified Ashworth Scale	
0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch or by minimal resistance at the end of the range of motion (ROM)when the affected part(s) is (are) moved in flexion or extension
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM
2	More marked increase in muscle tone through most of the ROM, but affected part(s) is (are) easily moved
3	Considerable increase in muscle tone, passive movement difficult
4	Affected part(s) is (are) rigid in flexion or extension
Modified Tardieu Scale	
X: Quality of movement mobilization	
0	No resistance throughout the course of the passive movement
1	Slight resistance throughout the course of passive movement, no clear catch at a precise angle
2	Clear catch at a precise angle, interrupting the passive movement, followed by release
3	Fatigable clonus with less than 10 s when maintaining the pressure and appearing at the precise angle
4	Unfatigable clonus with more than 10 s when maintaining the pressure and appearing at a precise angle
5	Joint is fixed
V: Measurements take place in three different velocities	
V1	As slow as possible
V2	Speed of limb segment falling under gravity
V3	As fast as possible
Y: Angle of catching (muscle reaction)	

Regarding treatments available to manage spasticity, the most commonly used are pharmacological drugs. Most pharmacological treatments are targeting the reduction of reflex activity by decreasing the release of excitatory neurotransmitters (glutamate, monoamines) or by potentiating the activity of inhibitory neurotransmitters (GABA, glycine) [26]. Baclofen, a GABAb receptor agonist, is one of the most widely used oral antispastic drug [27]. It reduces spasticity by enhancing presynaptic inhibition at the spinal level [15]. Some drugs act by increasing the affinity of GABA to its receptor complex (diazepam, clonazepam) or miming the GABA structure (gabapentin), while others take action at the muscular level (dantrolene, phenol, botulinum toxin) [10]. Intrathecal baclofen is another type of treatment against spasticity. In this case, baclofen is delivered by an implantable pump directly into the spinal fluid, aiming to have more direct effects while less side effects (e.g., sleepiness). Moreover, it appears to improve the level of consciousness and not only on a motor side but also regarding visual pursuit, object-related eye movements, and verbalization attempts [28, 29]. However, no controlled clinical

trials have been done to assess the effect of baclofen in a large cohort of patients with DOC, and the mechanisms underlying these behavioral effects have to be further investigated.

Beside pharmacological treatments, various non-pharmacological treatments exist, including physical therapy (especially stretching) [30], occupational therapy [31], orthoses [32], transcutaneous electrical nerve stimulation [33], cortical activation by thalamic stimulation [34], and surgical interventions [10]. However, all these treatments tend to reduce the symptoms of spasticity and not the source of spasticity itself. This can be explained by the lack of understanding regarding the exact pathophysiology of spasticity.

Spasticity in Patients with Disorders of Consciousness (DOC)

Pathophysiology

Processes underlying spasticity have not been fully understood yet, and its pathophysiology is multifactorial. Physiologically, muscle overactivity and pathological reflex responses to peripheral inputs such as cutaneous stimuli or muscle stretch might be the consequence of an anarchic reorganization of the CNS after a brain lesion [35, 36].

It is also known that central motor lesions are associated with loss of supraspinal control leading to impaired patterns of spinal reflexes [1]. On the other hand, intramuscular changes such as alterations of the collagen tissue, change in muscle fiber type, or loss of sarcomeres result in a spastic muscle pattern [37, 38]. Based on experimental animal models, spasticity would result from an imbalance between the inhibitory lateral reticulospinal tract and the excitatory medial reticulospinal and vestibulospinal tracts [39].

The location of the lesion(s) plays, of course, a determining role [40]. Damage of the cerebral cortex, cerebellum, and basal ganglia likely results in the abnormal muscle tone and motor patterns in patients with DOC [41]. The clinical signs of spasticity are due to a lesion of the UMNs (as part of the UMN syndrome) which include supraspinal inhibitory and excitatory fibers controlling spinal reflex activity. These UMNs are motor neurons starting in the motor cortical regions (Brodmann areas 4 and 6) or in the brain stem. However, spasticity emerges not only as a consequence of pyramidal tract lesion but due to parapyramidal fiber (e.g., dorsal/lateral reticulospinal tract) damages as well [35].

Due to these central lesions, patients may suffer from paralysis or paresis defined as *decreased voluntary motor unit recruitment* [42]. Beside the lesion itself, spasticity may be influenced by other non-neurological factors. Indeed, patients with DOC are mostly confined to bed, and many of them have lost voluntary motor movements. We observe immobilization in the one hand and disuse in the other hand.

While immobilization is a peripheral situation of lack of passive or active movement around a joint, disuse is a central situation of lack of voluntary command to this joint. These two different phenomena tend to occur together and have devastating motor consequences.

Patients are thus immobilized with their muscles in a shortened position which causes a reduction in longitudinal tension. This way, the muscles will lose mass and sarcomeres while accumulating connective tissue and fat [43, 44] leading to an exacerbation of muscle contracture. In addition, the loss of gravity effects (weight-bearing and counter-resistance activity) will major these phenomena [45] and reduce bone mineralization by stimulating catabolic responses of the musculoskeletal system [46]. Muscles which are maintained in a shorter position adapt to this resting length, and the amount of sarcomeres decreases and reorganizes in order to develop maximal tension at this new reduced length [47]. Not only the muscle is involved but the myotendinous junction endures a decrease in its tensile strength as well as due to a reduction in local vascular density and degenerative changes [48, 49]. This may also occur in patients encountering immobilization without neurological lesion (e.g., cast, burn). In patients with a CNS lesion, after a few weeks, the emergence of muscle overactivity becomes then an additional mechanism which will aggravate the contractures (defined as *loss of range of motion in a joint to a degree that impedes activities of daily living* [50]). If not treated, this decreasing passive muscle extensibility will lead to an acquired loss of ROM up to a permanent joint fixation [7, 51].

Afterward, progressive supraspinal and spinal rearrangements will give rise to muscle overactivity (defined by "increased involuntary motor unit recruitment" [36]). It progressively appears when the central execution of voluntary command is disrupted and represents another aggravating factor. Spastic overactivity as defined by Gracies [36] includes spasticity, spastic dystonia, and spastic cocontraction which are distinguished by their primary triggering factor (i.e., phasic muscle stretch, tonic muscle stretch, and volitional command, respectively). The precise pathophysiology of these excessive responses is still incompletely understood [5]. Logically, all these phenomena (paresis, contracture, and muscle overactivity) never present a symmetrical distribution between agonist and antagonist muscles, leading to torque imbalances around joints and deformities. As patients with DOC present a paresis that is aggravated by disuse due to the lack of voluntary command, the therapeutic challenge is to break the vicious cycle paresis—disuse—further paresis [42] (Fig. 7.1).

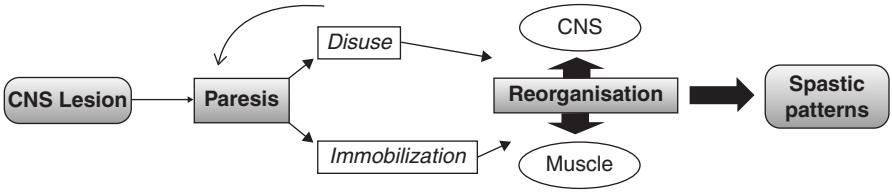

Fig. 7.1 Pathophysiology of spastic patterns (spasticity, spastic dystonia, spastic cocontractions)

Clinical Picture

In patients suffering from spasticity, the stretch reflexes are preserved and potentially accentuated [38]. Indeed, for a given velocity, stretch responses are increased and appear at a lower threshold compared to healthy subjects [39]. In some extreme cases, muscle contracture can be permanent, leading to a complete joint fixation. Regarding patients with DOC, they seldom fit in one particular clinical setting.

The first issue is to distinguish spasticity from rigidity. Rigidity is a form of plastic hypertonia arising from remodeling occurring in the basal ganglia [52]. It does not depend upon the speed of the muscle stretch and is not associated with other positive UMN signs such as hyperreflexia or spasms as spasticity does [35]. Therefore, it may be difficult to differentiate these two clinical entities since patients with DOC often show lesions involving extended areas responsible for the emergence of various forms of hypertonia. In addition, spasticity may often be associated with dystonia, which are sustained abnormal postures while the subject is at rest, due to basal ganglia lesions as well [53, 54]. Thus, spasticity is not necessarily the only dysfunctional motor pattern in patients with DOC. It is therefore difficult to assess it electively since it can be occulted by rigidity and/or dystonia.

Since these patients rarely demonstrate voluntary movements, an adaptive muscle shortening occurs as a consequence of this immobilization. This maladaptation contributes to a decrease in passive muscle extensibility, and, thus, passive movement will demonstrate a resistance. If muscle shortening is not treated, a permanent loss in ROM may occur and can further lead to joint deformation. Consequently, patients may have higher difficulties to initiate a movement and thereby to demonstrate a sign of consciousness [42].

This loss in ROM will in turn lead to joint retraction, due also to many other phenomena occurring together in the involved articular structures (e.g., adherence of fibrofatty connective tissue to cartilage surfaces, atrophy of cartilage, or regional osteoporosis) [55, 56]. The most often affected joints of brain injury survivors include the elbows, wrists, hips, knees, and ankles [57] (Fig. 7.2). Two stereotypic

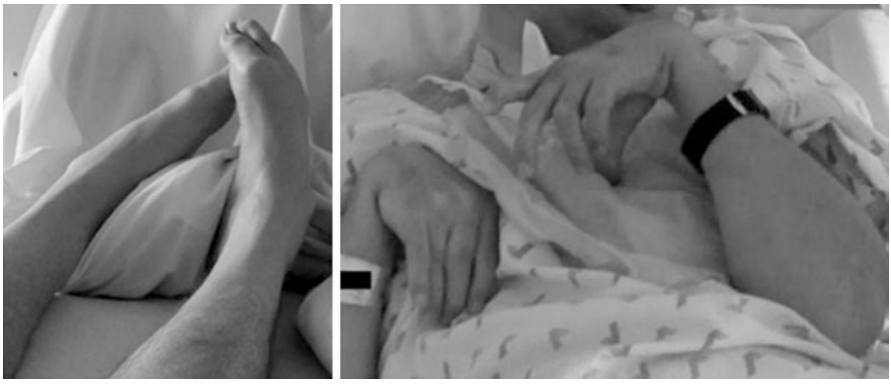

Fig. 7.2 Equinovarus feet (*left*) and decorticate spastic pattern (*right*) (from Thibaut et al. [10])

motor patterns due to different lesions' localizations are frequently observed. The first one is the decortication spastic pattern, due to subcortical lesions, which consists of a flexion of the upper limb and an extension of the lower limbs. The second one is the decerebration spastic pattern, due to brainstem lesions, which consists of an extension of both upper and lower limbs. However, the spastic patterns observed in patients with DOC are quite heterogeneous. While some suffer from spasticity in one side of the body, others have lower limbs bilaterally affected. There is no such "typical" pattern observed with patients with DOC as in poststroke hemiplegic patients (e.g., upper limb in internal rotation and adduction of the shoulder coupled with flexion of the wrist and the fingers [58]).

Muscle contractures are likely to appear especially if spasticity affects a joint in a shortened position [59]. Yet, while some authors allege that spasticity will lead to contractures [60, 61], in some patients, contractures may actually potentiate spasticity by amplifying the stretch reflex [62]. This hypothesis is based on the fact that the muscle shortening (due to the contracture) would alter the stretching effects [7]. While the thigh relationship between these two motor dysfunctions is clear, the exact interaction between them remains to be determined.

Considering the important difficulties for patients with DOC to express potential pain and their almost permanent immobile position in bed, which may increase side effects, prevention and treatment of spasticity need to be a critical part in their daily management [63], in order to reduce muscle tone, improve ROM and joint positioning, and thus facilitate the rehabilitation [26], as well as avoiding joint deformity and pain.

Patients with DOC Versus Stroke or Moderate TBI

In some clinical situations, spasticity is not problematic but may help hemiplegic patients to conserve their walking ability. Sometimes, indeed, it helps the patient to supply other weak muscles and allows to stand, to grab something, or to walk [1, 6]. Nevertheless, spasticity in patients with DOC, due to sustained immobilization [42] and lack of voluntary movements and communication, is a serious issue that needs to be managed as it is detected. Indeed, a loss in ROM is frequently observed, with various levels, in patients in UWS or MCS [64]. As mentioned above, the consequences related to spasticity (e.g., retractions, pain, and movement's limitation) may negatively impact patients' rehabilitation and quality of life. Besides, the presence of spasticity and thus the alteration of the motor function may potentially unable the patient to show subtle signs of consciousness, which will alter the diagnosis [65, 66].

One main difference between patients with DOC and patients who have suffered from a stroke is the lesion's location and extent. Indeed, while patients with stroke suffer from a typical and focal lesion, patients with DOC usually have far more extensive lesions, involving both cortical and deeper brain regions as well as subcortical areas [67]. Taking this into account, it may be difficult to

allocate some specific areas to the emergence of spasticity because of the intricacies of the lesions and the fact that some cortical lesions may be occulted by deeper regions' damages. As said above, from an anatomical point of view, lesions of the pyramidal tract are thought to be involved in the development of spasticity [68]. This neural pathway classically includes the brainstem, the cortex of the primary, secondary, and supplementary motor area, and the spinal cord. However, the pyramidal tract is far from being the only area of interest involved in the UMN syndrome which can be involved in the development of spasticity. The parapyramidal fibers have an important role as well since they pass very closely with the upper motor neurons and include inhibitory and excitatory pathways afferent on the spinal reflexes [35].

Patients suffering from a chronic stroke demonstrate a combination of spastic muscle hypertonia and an excess in muscle activity measured by EMG [69]. This can be measured by the responses to electrical (Hoffman reflex or H-reflex) or mechanical stimuli (Tendon reflex or T-reflex). The H-reflex allows assessing the alpha motoneuron's excitability and is often higher in patients presenting spasticity [10]. However, patients with DOC may not necessarily show this association of hyperactivity and hypertonia in the muscles since the EMG responses (e.g., the H-reflex) reflect the damage of focal lesions (such as in stroke) which may be occulted by more diffuse lesions (e.g., cortical and subcortical lesions) in patients with DOC. The pathophysiology of spasticity in DOC has to be further investigated, with the help of magnetic resonance imaging (MRI), for instance, in order to assess which specific structural lesions are often observed.

Regarding patients who had a spinal cord lesion, they will classically show the most severe signs of spasticity as compare to patients who had a stroke or other supraspinal lesions [16]. In the case of a spinal cord lesion, both inhibitory and excitatory pathways are abolished. Supraspinal lesion only withdraws cortical facilitation of the inhibitory pathways, which leads to mildly reduced inhibitory drive and less severe clinical signs [35]. Overall, cortical lesions observed in patients with DOC or stroke result in some degree of spasticity, hyperreflexia, and clonus, but these symptoms are less severe as compared to what is seen after a spinal cord lesion where the Wallerian degeneration after the anatomical disruption of the motor neurons leads to a major abnormal motor pattern [16, 70].

How to Treat Spasticity in Patients with DOC

While it is known that the care and rehabilitation of patients with DOC are time-demanding and can be expensive, there is still a lack of scientific evidence to guide their rehabilitation [15, 71]. Most of the time, physiotherapy treatment of spasticity includes passive range of motion and passive muscle stretch. Schmit and colleagues [72] investigated the effects on spasticity of repeated passive movements in flexion and extension of the elbow. They found out that the stretch reflex torque and EMG

responses were significantly reduced after 20–30 sequential flexion-extension movements (at constant velocity with a 10-s hold between flexion and extension) showing the potential positive impact of mobilization associated with stretching on muscle spasticity. Passive muscle stretch includes several modalities in order to hold the muscle in a lengthened position (e.g., by a therapist, a splint or orthosis, a cast, and a standing frame). Three studies showed that passive muscle stretch from 10 to 35 min seems effective on adults with cerebrovascular accident (CVA) and TBI and on children with cerebral palsy [73–75]. Short passive stretching exercises (20–60 s) in children with cerebral palsy who suffered from spasticity also seem to be effective for reducing knee flexion contractures [76]. However, according to a recent Cochrane Review, the effectiveness of stretch for the management of contractures in UWS or MCS patients is not well established yet [77].

Other studies demonstrated the effectiveness of serial casting (process of applying and removing corrective casts in succession [57]) by an increase of joint ROM and a reduction of spasticity following the placement of gradual corrective casts for 4–6 weeks, 24 h a day [78]. According to Mortenson and Eng [79], the use of casts would be the best technique to improve passive ROM. However, it should be noted that this conclusion is not shared by all the researchers [80, 81] due, in part, to the lack off randomized clinical trials on patients with CNS disorders. Besides, it is recommended to correctly position the joint, approximately 5° less than maximal endpoint of ROM, in order to avoid triggering a reflexive increase in muscle hypertonicity [57]. Yet, chronic patients with DOC usually present severe reduction of ROM. Furthermore, they often are at highest risk, as compared to other populations of patients with neurological condition, for skin problems, such as irritation or bedsores [82], and, thus, casting seems less likely to be adapted for this specific population of patients.

Many reviews and studies emphasized the lack of clinical effectiveness of passive muscle stretch [78, 83], and none of them actually suggest new rehabilitation approaches. The evidence of the efficacy of these interventions remains poor although they are used in a daily routine by caregivers since patient's collaboration is not required.

Rigid splints are widely used for patients with poststroke spasticity [84, 85] and for children with cerebral palsy [86] even if their tolerability for long periods is not optimal [32]. Patients in UWS or MCS often show severe signs of spasticity with significant contractures; therefore, they need a more appropriate way to stretch and relax their spastic muscles without risking them to be injured. A recent study [87] proposed an alternative by applying hand-rolled soft splints on the upper limb of chronic spastic patients with DOC (Fig. 7.3). The aim was to decrease spasticity, improve hand opening, and compare the effectiveness of manual stretching against soft splints on upper limb spasticity. Both manual stretching and soft splints showed positive impact on patients' spasticity, while only soft splints were able to increase hand opening, which is significant for patients' hygiene, to avoid maceration or even injuries.

As in previous studies [73, 78], the effects seemed to be transient by lasting more or less 30 min but disappeared after 60 min. The main advantages of soft splints

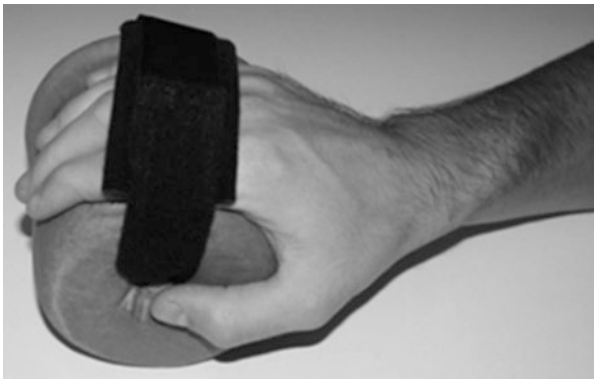

Fig. 7.3 Example of soft splint (from Thibaut et al. [87])

compared to rigid splints are their easy application and the low risk of causing pain or injuries since they are flexible and allow muscle contraction and grasping reflex. Therefore, they might be a valuable option for chronic patients with DOC suffering from upper limb spasticity.

A more invasive perspective is the botulinum toxin injection. National clinical guidelines identified the benefits of botulinum toxin with a program of stretching and physiotherapy (including splinting) for adult patients suffering from poststroke spasticity [88]. Regarding its use for patients with DOC, Belgian researchers investigated the effects of botulinum toxin type A (BTX-A) for the management of spasticity in children with an acquired brain injury [89]. One of the three subgroups consisted of young children with severe spastic quadriparesis and impaired consciousness. In this group, bilateral intramuscular BTX-A injections (~4.19 IU/kg) in the hip adductors, knee, and plantar flexors showed improvement in spasticity and ROM (average 1.75 point decrease in MAS and +7° goniometry), with the higher effects at 3 months posttreatment. The authors concluded that intramuscular BTX-A injections in combination with orthotic devices may be considered as an effective treatment to manage severe spasticity in chronic patients with severe acquired brain injuries. These results are in line with those of Yablon and colleagues [90] who showed that BTX-A significantly improves spasticity and ROM in the distal upper limb of both acute (less than 1 year after the lesion) and chronic patients (more than 1 year after the lesion) with moderate or severe TBI. However, botulinum toxin requires careful use because of its toxicity [91]. It is not manageable to perform injections in a high amount of muscles; only a few can be targeted which restricts the efficiency of this method.

Further randomized clinical trials investigating both pharmacological and non-pharmacological treatment have to be performed in this specific population of patients with chronic DOC. Naturally, there are as many clinical settings as the amount of patients suffering from spasticity. Therefore, the best clinical practice for patients with DOC is naturally individualized, multidisciplinary, and patient centered [92]. However, providing evidence-based guidelines based on randomized clinical trials is a difficult task since this population of patients is highly heterogeneous

which makes the comparison between groups very difficult. Crossover designs and single-subject designs seem to be a more appropriate option for patients with DOC [78].

Clinical Recommendations

Since the process of muscle contracture initiating muscular atrophy is acute (occurring within the first 6 h of immobilization) [42, 93], early mobilization (passive ROM) is crucial in order to avoid premature complications. Although the main objective in the intensive care unit is to keep a sufficient lung function, the motor issue should not be put aside. Actually, any type of treatment, pharmacological or non-pharmacological, should be started early, as soon as muscle overactivity is distributed diffusely and causes clinical disability, in order to prevent permanent articular deformities or muscle contractures. Afterward, even if it is often unknown in the acute setting if the patients will or not fully recover, an early post-acute care should be provided in a specialized rehabilitation center where patients can be properly assessed, and a suitable care program can be established. Further, at the chronic stage, using soft and comfortable splints to decrease spasticity should be recommended [87], in addition to the existent treatments, since patients with DOC are not able to communicate their pain feelings.

Physiotherapists will have a key role to play although little is known about the effect of intensity of physiotherapy on motor outcomes [15]. They are strongly involved in the patient's care and rehabilitation by seeing them nearly every day for respiratory physiotherapy, stretching, positioning, multisensory stimulation programs, and much more, in order to enhance the comfort and stimulate patients' arousal. Regarding spasticity in particular, physiotherapists have to position and stretch them right for several hours a day in order to manage the muscular tone, to avoid any contracture and to maintain the skin integrity [94–96]. In order to effectively improve the function and comfort of patients with DOC, the physiotherapist's interventions have to be frequent and of prolonged duration. However, the cost for the social security is high. Future studies have to clarify the minimal but sufficient amount of physiotherapy in acute and chronic situations and establish evidence-based guidelines for the spasticity management.

Naturally, a multidisciplinary approach combining physical, pharmacological, and surgical treatment interventions is needed to manage this spasticity properly [82]. Not only the therapists but the families have a significant role to play [97], and they should be encouraged to take part in the care by gently stretching, massaging, and stimulating their relatives every day, beside physical therapy or oral therapy sessions. At a prolonged chronic stage, the emphasis is more on maintaining quality of life than preserving function toward the expectation of future recovery since the chances of recovery are less likely to occur [94].

Conclusion

Patients with DOC usually need important and specific management (e.g., medical care, nursing, rehabilitation, and speech therapy). They may require up to 7 h of care per day due to their (almost) entire dependency [98]. As said above, spasticity concerns a majority of these patients and does not only induce pain but may also lead to severe orthopedic deformities which increase the care difficulty. In addition to the induction of pain, ankylosis, and muscle weakness, the presence of spasticity and thus the alteration of the motor function may not only interfere with rehabilitation but potentially unable the patient to show several signs of consciousness as well, which can lead to misdiagnosis [99]. Appropriate treatment and careful follow-up are thus required in order to enhance patients' daily life. Over time, spasticity management may become more comfort care and less curative, but it has to stay in the medical care priorities.

References

1. Dietz V, Sinkjaer T. Spastic movement disorder: impaired reflex function and altered muscle mechanics. Lancet Neurol. 2007;6:725–33. doi:10.1016/S1474-4422(07)70193-X.
2. Lance JW. Spasticity: disorders motor control. In: Feldman RG, Young RP, Koella WP, editors. Symposium synopsis. Miami, FL: Year Book Medical Publishers; 1980.
3. Pandyan AD, Gregoric M, Barnes MP. Spasticity: clinical perceptions, neurological realities and meaningful measurement. Disabil Rehabil. 2005;27:2–6.
4. Tardieu G, Shentoub S, Delarue R. A la recherche d'une technique de mesure de la spasticité. Rev Neurol. 1954;91:143–4.
5. Young RR. Spasticity: a review. Neurology. 1994;44:S12–20.
6. Burke D, Wissel J, Donnan GA. Pathophysiology of spasticity in stroke. Neurology. 2013;80:S20–6. doi:10.1212/WNL.0b013e31827624a7.
7. O'Dwyer NJ, Ada L, Neilson PD. Spasticity and muscle contracture following stroke. Brain. 1996;119(Pt 5):1737–49.
8. Zorowitz RD, Gillard PJ, Brainin M. Poststroke spasticity: sequelae and burden on stroke survivors and caregivers. Neurology. 2013;80:S45–52. doi:10.1212/WNL.0b013e3182764c86.
9. Blicher JU, Nielsen JF. Does long-term outcome after intensive inpatient rehabilitation of acquired brain injury depend on etiology? NeuroRehabilitation. 2008;23:175–83.
10. Thibaut A, Chatelle C, Ziegler E, et al. Spasticity after stroke: physiology, assessment and treatment. Brain Inj. 2013;27:1093–105. doi:10.3109/02699052.2013.804202.
11. Plum F, Posner JB. The diagnosis of stupor and coma. Contemp Neurol Ser. 1972;10:1–286.
12. Laureys S, Boly M. Unresponsive wakefulness syndrome. Arch Ital Biol. 2012;150:31–5. doi:10.4449/aib.v150i2.1407.
13. Georgiopoulos M, Katsakiori P, Kefalopoulou Z, et al. Vegetative state and minimally conscious state: a review of the therapeutic interventions. Stereotact Funct Neurosurg. 2010;88:199–207. doi:10.1159/000314354.
14. Giacino JT, Ashwal S, Childs N, et al. The minimally conscious state: definition and diagnostic criteria. Neurology. 2002;58:349–53.
15. Leong B. The vegetative and minimally conscious states in children: spasticity, muscle contracture and issues for physiotherapy treatment. Brain Inj. 2002;16:217–30. doi:10.1080/02699050110103283.

16. Ward AB. A literature review of the pathophysiology and onset of post-stroke spasticity. Eur J Neurol. 2012;19:21–7. doi:10.1111/j.1468-1331.2011.03448.x.
17. Mayer NH, Esquenazi A. Muscle overactivity and movement dysfunction in the upper motoneuron syndrome. Phys Med Rehabil Clin N Am. 2003;14:855–83.
18. Sunnerhagen KS, Olver J, Francisco GE. Assessing and treating functional impairment in poststroke spasticity. Neurology. 2013;80:S35–44. doi:10.1212/WNL.0b013e3182764aa2.
19. Brashear A, Zafonte R, Corcoran M, et al. Inter- and intrarater reliability of the Ashworth Scale and the Disability Assessment Scale in patients with upper-limb poststroke spasticity. Arch Phys Med Rehabil. 2002;83:1349–54.
20. Ghotbi N, Nakhostin Ansari N, Naghdi S, Hasson S. Measurement of lower-limb muscle spasticity: intrarater reliability of Modified Ashworth Scale. J Rehabil Res Dev. 2011;48:83–8.
21. Yelnik AP, Simon O, Parratte B, Gracies JM. How to clinically assess and treat muscle overactivity in spastic paresis. J Rehabil Med. 2010;42:801–7. doi:10.2340/16501977-0613.
22. Voerman GE, Gregoric M, Hermens HJ. Neurophysiological methods for the assessment of spasticity: the Hoffmann reflex, the tendon reflex, and the stretch reflex. Disabil Rehabil. 2005;27:33–68.
23. Kakebeeke T, Lechner H, Baumberger M, et al. The importance of posture on the isokinetic assessment of spasticity. Spinal Cord. 2002;40:236–43.
24. Lamontagne A, Malouin F, Richards CL, Dumas F. Evaluation of reflex- and nonreflex-induced muscle resistance to stretch in adults with spinal cord injury using hand-held and isokinetic dynamometry. Phys Ther. 1998;78:964–75. discussion 976–8
25. Biering-Sørensen F, Nielsen JB, Klinge K. Spasticity-assessment: a review. Spinal Cord. 2006;44:708–22. doi:10.1038/sj.sc.3101928.
26. Abbruzzese G. The medical management of spasticity. Eur J Neurol. 2002;9:30–4. doi:10.1046/j.1468-1331.2002.0090s1030.x.
27. Richard I, Menei P. Intrathecal baclofen in the treatment of adult spasticity. Neurosurg Focus. 2007;21:e5. doi:10.3171/foc.2006.21.2.6.
28. Pistoia F, Sacco S, Sarà M, et al. Intrathecal Baclofen: effects on spasticity, pain, and consciousness in disorders of consciousness and locked-in syndrome. Curr Pain Headache Rep. 2015; doi:10.1007/s11916-014-0466-8.
29. Margetis K, Korfias SI, Gatzonis S, et al. Intrathecal baclofen associated with improvement of consciousness disorders in spasticity patients. Neuromodulation. 2014;17:699–704. doi:10.1111/ner.12147.
30. Bovend'Eerdt TJ, Newman M, Barker K, et al. The effects of stretching in spasticity: a systematic review. Arch Phys Med Rehabil. 2008;89:1395–406. doi:10.1016/j.apmr.2008.02.015.
31. Goldstein EM. Spasticity management: an overview. J Child Neurol. 2001;16:16–23.
32. Feldman PA. Upper extremity casting and splinting. In: Glenn MB, Whyte J, editors. The Practical Management of Spasticity in Children and Adults. Philadelphia, PA: Lea and Febiger; 1990.
33. Sahin N, Ugurlu H, Albayrak I. The efficacy of electrical stimulation in reducing the poststroke spasticity: a randomized controlled study. Disabil Rehabil. 2012;34:151–6. doi:10.3109/09638288.2011.593679.
34. Magrassi L, Maggioni G, Pistarini C, et al. Results of the prospective study (CATS) on the effects of thalamic stimulation in minimally conscious and vegetative state patients. J Neurosurg. 2016;125(4):972–81.
35. Sheean G. The pathophysiology of spasticity. Eur J Neurol. 2002;9(Suppl 1):3–61.
36. Gracies JM. Pathophysiology of spastic paresis II: emergence of muscle overactivity. Muscle Nerve. 2005;31:552–71.
37. Lieber RL, Steinman S, Barash IA, Chambers H. Structural and functional changes in spastic skeletal muscle. Muscle Nerve. 2004;29:615–27. doi:10.1002/mus.20059.
38. Castle ME, Reyman TA, Schneider M. Pathology of spastic muscle in cerebral palsy. Clin Orthop Relat Res. 1979;142:223–33.
39. Brown P. Pathophysiology of spasticity. J Neurol Neurosurg Psychiatry. 1994;57:773–7.

40. Ivanhoe CB, Reistetter TA. Spasticity: the misunderstood part of the upper motor neuron syndrome. Am J Phys Med Rehabil. 2004;83:S3–9.
41. Kinney H, Samuels M. Neuropathology of the persistent vegetative state. A review. J Neuropathol Exp Neurol. 1994;53(6):548–58.
42. Gracies JM. Pathophysiology of spastic paresis. I: paresis and soft tissue changes. Muscle Nerve. 2005;31:535–51. doi:10.1002/mus.20284.
43. Tardieu C, Tardieu G, Colbeau-Justin P, et al. Trophic muscle regulation in children with congenital cerebral lesions. J Neurol Sci. 1979;42:357–64.
44. Williams PE, Goldspink G. Connective tissue changes in immobilised muscle. J Anat. 1984;138(Pt 2):343–50.
45. Berg HE, Larsson L, Tesch PA. Lower limb skeletal muscle function after 6 wk of bed rest. J Appl Physiol. 1997;82:182–8.
46. Alzghoul MB, Gerrard D, Watkins BA, Hannon K. Ectopic expression of IGF-I and Shh by skeletal muscle inhibits disuse-mediated skeletal muscle atrophy and bone osteopenia in vivo. FASEB J. 2004;18:221–3. doi:10.1096/fj.03-0293fje.
47. Williams PE, Goldspink G. Changes in sarcomere length and physiological properties in immobilized muscle. J Anat. 1978;127:459–68.
48. Kvist M, Hurme T, Kannus P, et al. Vascular density at the myotendinous junction of the rat gastrocnemius muscle after immobilization and remobilization. Am J Sports Med. 1995;23:359–64. doi:10.1177/036354659502300320.
49. Kannus P, Jozsa L, Kvist M, et al. The effect of immobilization on myotendinous junction: an ultrastructural, histochemical and immunohistochemical study. Acta Physiol Scand. 1992;144:387–94. doi:10.1111/j.1748-1716.1992.tb09309.x.
50. Yarkony GM, Sahgal V (1987) Contractures. A major complication of craniocerebral trauma. Clin Orthop Relat Res (219):93–96.
51. Sinkjaer T, Toft E, Larsen K, et al. Non-reflex and reflex mediated ankle joint stiffness in multiple sclerosis patients with spasticity. Muscle Nerve. 1993;16:69–76. doi:10.1002/mus.880160112.
52. Delwaide P, Pepin J. Projections from basal ganglia to tegmentum: a subcortical route for explaining the pathophysiology of Parkinson's disease signs? J Neurol. 2000;247(Suppl 2):II75–81.
53. Ben Smaïl D, Kieffer C, Bussel B. Evaluation clinique de la spasticité. Neurochirurgie. 2003;49:190–8.
54. Trompetto C, Marinelli L, Mori L. Pathophysiology of spasticity: implications for neurorehabilitation. Biomed Res Int. 2014;2014:354906.
55. Liebesman JL, Cafarelli E. Physiology of range of motion in human joints: a critical review. Crit Rev Phys Rehabil Med. 1994;6:131.
56. Bell KR, Vandenborne K. Contracture and limb deformities. In: Lazar RB, editor. Principles of neurologic rehabilitation. New York: McGraw-Hill; 1998. p. 309–28.
57. Evans CD. Rehabilitation after severe head injury. New York: Churchill Livingstone; 1981.
58. Hefter H, Jost WH, Reissig A, et al. Classification of posture in poststroke upper limb spasticity: a potential decision tool for botulinum toxin A treatment? Int J Rehabil Res. 2012;35:227–33. doi:10.1097/MRR.0b013e328353e3d4.
59. Malhotra S, Pandyan AD, Day CR, et al. Spasticity, an impairment that is poorly defined and poorly measured. Clin Rehabil. 2009;23:651–8. doi:10.1177/0269215508101747.
60. Harburn K, Potter P. Spasticity and contractures. Phys Med Rehabil. 1993;7:113–22.
61. Botte MJ, Nickel VL, Akeson WH (1988) Spasticity and contracture. Physiologic aspects of formation. Clin Orthop Relat Res (233):7–18.
62. Brainin M. Poststroke spasticity: treating to the disability. Neurology. 2013;80:S1–4.
63. Pistoia F, Sacco S, Sarà M, Carolei A. The perception of pain and its management in disorders of consciousness. Curr Pain Headache Rep. 2013;17:374. doi:10.1007/s11916-013-0374-3.
64. Pilon M, Sullivan SJ. Motor profile of patients in minimally responsive and persistent vegetative states. Brain Inj. 1996;10:421–37.

65. Formisano R, Pistoia F, Sarà M. Disorders of consciousness: a taxonomy to be changed? Brain Inj. 2011;25:638–9. doi:10.3109/02699052.2011.572948.
66. Pistoia F, Sarà M. Is there a Cartesian renaissance of the mind or is it time for a new taxonomy for low responsive states? J Neurotrauma. 2012;29:2328–31. doi:10.1089/neu.2009.1257.
67. Di Perri C, Stender J, Laureys S, Gosseries O. Functional neuroanatomy of disorders of consciousness. Epilepsy Behav. 2014;30:28–32. doi:10.1016/j.yebeh.2013.09.014.
68. Sommerfeld DK, Eek EU, Svensson AK, et al. Spasticity after stroke: its occurrence and association with motor impairments and activity limitations. Stroke. 2004;35:134–9. doi:10.1161/01.STR.0000105386.05173.5E.
69. Dietz V, Trippel M, Berger W. Reflex activity and muscle tone during elbow movements in patients with spastic paresis. Ann Neurol. 1991;30:767–79. doi:10.1002/ana.410300605.
70. Ditunno JF, Little JW, Tessler A, Burns AS. Spinal shock revisited: a four-phase model. Spinal Cord. 2004;42:383–95. doi:10.1038/sj.sc.3101603.
71. Elliott L, Walker L. Rehabilitation interventions for vegetative and minimally conscious patients. Neuropsychol Rehabil. 2007;15:480–93. doi:10.1080/09602010443000506.
72. Schmit BD, Dewald JPA, Rymer WZ. Stretch reflex adaptation in elbow flexors during repeated passive movements in unilateral brain-injured patients. Arch Phys Med Rehabil. 2000;81:269–78. doi:10.1053/apmr.2000.0810269.
73. Tremblay F, Malouin F, Richards CL, Dumas F. Effects of prolonged muscle stretch on reflex and voluntary muscle activations in children with spastic cerebral palsy. Scand J Rehabil Med. 1990;22:171–80.
74. Hale LA, Fritz VU, Goodman M. Prolonged static muscle stretch reduces spasticity. South African J Physiother. 1995;51:3–6.
75. Al-Zamil ZM, Hassan N, Hassan W. Reduction of elbow flexor and extensor spasticity following muscle stretch. Neurorehabil Neural Repair. 1995;9:161–5.
76. McPherson JJ, Arends TG, Michaels MJ, Trettin K. The range of motion of long term knee contractures of four spastic cerebral palsied children. Phys Occup Ther Pediatr. 1984;4:17–34. doi:10.1080/J006v04n01_04.
77. Katalinic OM, Harvey LA, Herbert RD, et al (2010) Stretch for the treatment and prevention of contractures. Cochrane Database Syst Rev CD007455. doi:10.1002/14651858.CD007455.pub2
78. Leong B. Critical review of passive muscle stretch: implications for the treatment of children in vegetative and minimally conscious states. Brain Inj. 2002;16:169–83. doi:10.1080/02699050110103292.
79. Mortenson PA, Eng JJ. The use of casts in the management of joint mobility and hypertonia following brain injury in adults: a systematic review. Phys Ther. 2003;83:648–58.
80. Lannin NA, Novak I, Cusick A. A systematic review of upper extremity casting for children and adults with central nervous system motor disorders. Clin Rehabil. 2007;21:963–76. doi:10.1177/0269215507079141.
81. Singer BJ, Dunne JW, Singer KP, et al. Non-surgical management of ankle contracture following acquired brain injury. Disabil Rehabil. 2004;26:335–45. doi:10.1080/0963828032000174070.
82. Lehmkuhl LD, Thoi LL, Baize C, et al. Multimodality treatment of joint contractures in patients with severe brain injury: cost, effectiveness, and integration of therapies in the application of serial/inhibitive casts. J Head Trauma Rehabil. 1990;5:23–42.
83. NHS QIS Scotland Evidence Note. Manual passive stretching for adults with chronic neurological conditions who are unable to move their own joints. NHS Scotland. 2005.
84. Basaran A, Emre U, Karadavut KI, et al. Hand splinting for poststroke spasticity: a randomized controlled trial. Top Stroke Rehabil. 2012;19:329–37. doi:10.1310/tsr1904-329.
85. Shah S (2007) Wrist splint for upper motor neuron paralysis. Stroke 38:e74; author reply e75. doi:10.1161/STROKEAHA.107.488031
86. Gans BM, Erickson G, Simons D. Below-knee orthosis: a wrap-around design for ankle-foot control. Arch Phys Med Rehabil. 1979;60:78–80.

87. Thibaut A, Deltombe T, Wannez S, et al. Impact of soft splints on upper limb spasticity in chronic patients with disorders of consciousness: a randomized, single-blind, controlled trial. Brain Inj. 2015;29:830–6. doi:10.3109/02699052.2015.1005132.
88. Turner-Stokes L, Ashford S, Bhakta B, et al. Spasticity in adults: management using botulinum toxin: national guidelines. Physicians: London R. Coll; 2009.
89. van Rhijn J, Molenaers G, Ceulemans B. Botulinum toxin type A in the treatment of children and adolescents with an acquired brain injury. Brain Inj. 2005;19:331–5. doi:10.1080/02699050400013675.
90. Yablon SA, Agana BT, Ivanhoe CB, Boake C. Botulinum toxin in severe upper extremity spasticity among patients with traumatic brain injury: an open-labeled trial. Neurology. 1996;47:939–44.
91. Tsui JKC. Botulinum toxin as a therapeutic agent. Pharmacol Ther. 1996;72:13–24. doi:10.1016/S0163-7258(96)00091-5.
92. National Health and Medical Research Council. Ethical guidelines for the care of people in post-coma unresponsiveness (vegetative state) or a minimally responsive state. Canberra: National Health and Medical Research Council; 2008.
93. Booth FW. Effect of limb immobilization on skeletal muscle. J Appl Physiol. 1982;52:1113–8.
94. Royal College of Physicians. Prolonged disorders of consciousness: National clinical guidelines. London: Royal College of Physicians; 2013.
95. Tardieu C, Lespargot A, Tabary C, Bret MD. For how long must the soleus muscle be stretched each day to prevent contracture? Dev Med Child Neurol. 1988;30:3–10.
96. Hellweg S, Johannes S. Physiotherapy after traumatic brain injury: a systematic review of the literature. Brain Inj. 2008;22:365–73. doi:10.1080/02699050801998250.
97. Latchem J, Kitzinger J, Kitzinger C. Physiotherapy for vegetative and minimally conscious state patients: family perceptions and experiences. Disabil Rehabil. 2015;8288:1–8. doi:10.3109/09638288.2015.1005759.
98. Saoût V, Ombredane MP, Mouillie JM, et al. Patients in a permanent vegetative state or minimally conscious state in the Maine-et-Loire county of France: a cross-sectional, descriptive study. Ann Phys Rehabil Med. 2010;53:96–104. doi:10.1016/j.rehab.2010.01.002.
99. Shiel A, Gelling L, Wilson B, et al. Difficulties in diagnosing the vegetative state. Br J Neurosurg. 2004;18:5–7. doi:10.1080/02688690410001660625.

Chapter 8
Feasibility of Oral Feeding in Patients with Disorders of Consciousness

Audrey Maudoux, Ingrid Breuskin, Olivia Gosseries, Evelyne Mélotte, Caroline Schnakers, and Audrey Vanhaudenhuyse

A. Maudoux, M.D., Ph.D. (✉)
Oto-Rhino-Laryngology Head and Neck Surgery Department, University Hospital of Liège, Sart-Tilman-B35, 4000 Liège, Belgium

Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium
e-mail: audrey.maudoux@gmail.com

I. Breuskin, M.D., Ph.D.
Head and Neck Carcinologic Department, Gustave Roussy, University Paris-Saclay, Villejuif, France
e-mail: ingrid.breuskin@gustaveroussy.fr

O. Gosseries, Ph.D.
Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium
e-mail: ogosseries@ulg.ac.be

E. Mélotte
Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium

Physical Medicine Department, University Hospital of Liège, Sart-Tilman-B35, 4000 Liège, Belgium
e-mail: evelyne.melotte@chu.ulg.ac.be

C. Schnakers, Ph.D.
Department of Neurosurgery, University of California Los Angeles (UCLA), Los Angeles, CA, USA

Department of Research, Casa Colina Hospital and Centers for Healthcare, Pomona, CA, USA
e-mail: cschnakers@ucla.edu; cschnakers@casacolina.org

A. Vanhaudenhuyse, Ph.D.
Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium

Algology and Palliative Care Department, University Hospital of Liège, Sart Tilman B35, 4000 Liège, Belgium
e-mail: avanhaudenhuyse@chu.ulg.ac.be

C. Schnakers, S. Laureys (eds.), *Coma and Disorders of Consciousness*,
DOI 10.1007/978-3-319-55964-3_8

Abstract Eating and drinking are basic pleasures of life. However, the ease with which we perform these actions masks the complexity of the underlying neuronal control. According to several studies, dysphagia among subjects with severe brain injury is frequent. Faced with the difficult management of patients with an altered state of consciousness, the use of gustatory stimuli, as well as the rehabilitation of swallowing, could constitute an additional therapy, currently rarely considered. This review aims to summarize our current knowledge regarding the neural control of swallowing, to assess the role of awareness and willingness on swallowing control, and, finally, to establish the feasibility of oral feeding in patients with disorders of consciousness.

Introduction

Eating and drinking are basic pleasures of life, considered as natural to most of us. However, the ease with which we perform these actions masks the complexity of the underlying neuronal control. Various regions of the central nervous system, from brain stem to cortex, are involved in the realization of this complex sensorimotor sequence. Swallowing involves muscles of the face, tongue, pharynx, larynx, and esophagus, with a total of 26 pairs of muscles plus the unique superior longitudinal lingual muscle and five pairs of cranial nerves. The complexity of the underlying neural mechanism and the number of muscles and cranial nerves involved make the study of swallowing in animals and humans difficult. Although the assessment of dysphagia and rehabilitation techniques have been extensively studied, no major breakthrough in the understanding of the neurophysiological basis supporting the phenomenon has been provided.

Interest in the study of swallowing has increased in the past few years. Initially, groups of patients with neurological disorders (e.g., stroke) were studied. A precise anatomical study of brain lesions, using computed tomography scanner (CT scanner) or magnetic resonance imaging (MRI), was correlated with the clinical assessment in order to establish a relationship between the location of brain lesion and the presence and type of dysphagia. Subsequently, the development of functional imaging techniques allowed the study of swallowing in healthy volunteers. According to several studies, the frequency of dysphagia among subjects with severe brain injury varies between 25 and 61% [1–3]. These swallowing difficulties are mainly due to physiological deficits (affecting the swallowing mechanism) and impaired cognition. Faced with the difficult management of patients with altered state of consciousness, the use of gustatory stimuli, as well as swallowing rehabilitation, could constitute supplementary therapies [4]. Furthermore, it is of interest to assess whether or not the clinical swallowing evaluation could be used as a tool for neurological diagnosis or as a prognosis factor for consciousness recovery. The review presented here aims to summarize our current knowledge regarding the neural control of swallowing (whether initiated voluntarily or not), to assess the role of awareness and willingness on swallowing control, and, finally, to establish the feasibility of oral feeding in patients with disorders of consciousness.

Neurophysiology of Swallowing

Since Magendie in 1825, swallowing is classically divided into three parts: the oral, pharyngeal, and esophageal phases. The oral phase is usually described as voluntary, and the pharyngeal and esophageal phases (mainly under the control of the autonomic nervous system) are usually described as reflex (Fig. 8.1).

The Oral Phase

The oral phase is the only voluntary stage of swallowing. It is composed of the ingestion, mastication, and food insalivation. These steps lead to the formation of the bolus, which is then transported to the pharynx. During this phase, the oral cavity remains closed in order to contain the food. At the front, the contraction of the orbicularis oris muscle acts as the anterior sphincter. At the back, the velum, lowered against the

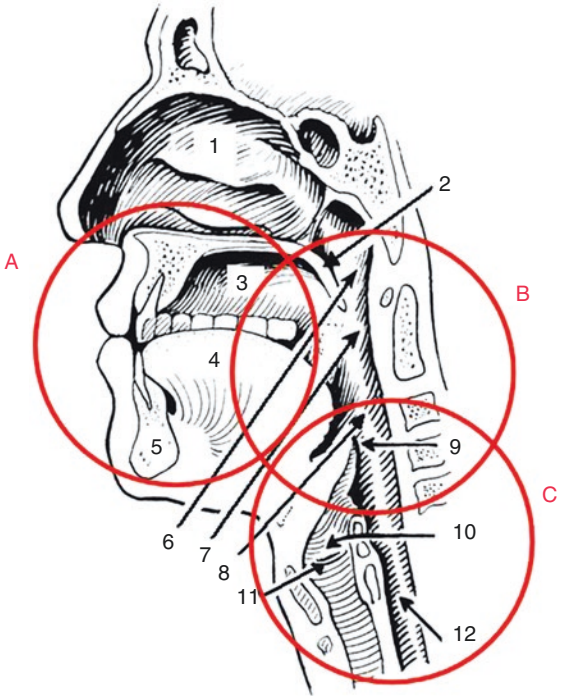

Fig. 8.1 The three phases of swallowing: *A* oral phase, *B* pharyngeal phase, *C* esophageal phase. *1* nasal cavity, *2* soft palate, *3* mouth, *4* tongue, *5* mandible, *6* nasopharynx, *7* oropharynx, *8* laryngopharynx, *9* epiglottis, *10* larynx, *11* vocal cords, *12* esophagus (Adapted from [5])

tongue, acts as the posterior sphincter. It prevents the early passage of food in the pharynx. During mastication, as the tongue and cheeks move food between them, the teeth crush, cut, and tear the aliments. The insalivation occurs during chewing. Insalivation has both a digestive role, due to the action of amylase, and a mechanical role by providing lubrication and cohesion to the bolus. During the propulsion step, the bolus is moved to the back of the oral cavity. When food reaches the *Wassilieff* area (a mucous membrane covering the soft palate, the base of the tongue, the vallecula, and the posterior pharyngeal wall), the pharyngeal phase of swallowing begins. Thus, the *Wassilieff* area delimits the transition from the oral phase to the second stage of swallowing—the pharyngeal phase. The oral phase varies in duration depending on taste, food consistency, environment, hunger, motivation, and the patient's level of consciousness. It relies on a good tongue mobility and the perfect function of numerous muscles: the suprahyoid muscles, the jaw-closing muscles (temporalis muscle, masseter muscle), the pterygoid and the infrahyoid muscles (allowing stabilization of the hyoid bone), the orbicularis oris muscle, and the palatoglossus muscles.

The Pharyngeal Phase

The swallowing reflex itself starts when the food reaches the pharyngeal space. It is followed by a series of events leading to the transportation of the bolus to the esophagus and to the protection of the airway. The pharyngeal phase includes three steps.

1. *Protection of the Nasopharynx and Larynx*
   The occlusion of the velopharyngeal sphincter aims to isolate the oropharynx from the nasopharynx. The elevation of the soft palate together with the approximation of the lateral pharyngeal walls avoids nasal reflux of food and liquid. Protection of lower airways is provided by the occlusion of the laryngeal sphincter (elevation of the larynx, closing of the vocal cord plane and the ventricular folds, anterior tilt of the arytenoids, and folding of the epiglottis over the glottis). The ascension of the larynx is critical. It protects the airway by positioning the larynx under the base of the tongue and by closing the laryngeal ventricles. It also promotes the opening of the upper esophageal sphincter (UES).
2. *Propulsion of the Bolus Through the Pharynx*
   The propulsion of the bolus is mainly provided by the posterior movement of the base of the tongue, pushing the bolus into the esophagus. To complete the hypopharyngeal draining, the pharyngeal constrictor muscles contract sequentially, achieving a peristaltic wave and pushing the food bolus from top to bottom.
3. *Upper Esophageal Sphincter Opening*
   During swallowing, the cricopharyngeal muscle relaxes, and the sphincter is pulled forward by contraction of suprahyoid muscles, allowing its opening. Finally, the pharyngeal phase ends, and the UES closes until the next swallowing.

The fine and synchronized movements of the different muscles involved are controlled by the brain stem via the central pattern generator (CPG).

The Esophageal Phase

The esophageal phase ensures the transfer of the bolus from the UES to the stomach. By working in sync, the two muscular layers of the esophagus (external longitudinal and inner circular layers) create the movements of peristalsis.

The Neurological Control

Swallowing requires a perfect coordination between all the aforementioned muscles. This is achieved through fine control of the central nervous system. Indeed, because the respiratory and digestive tracts cross in the pharynx, the slightest misstep in the sequence of swallowing may result in inhalation (the passage of part of the bolus into the airway). The main structure in charge of the neural control is the swallowing CPG. The CPG is located in the brain stem. It receives both sensory inputs from the periphery (oral cavity, pharynx, and larynx) and cortical afferents. The CPG integrates these informations, develops a motor program, and transmits the program to the motor neuron nuclei. The CPG is the organizer of the sequential activation of motor neurons involved in swallowing (Fig. 8.2).

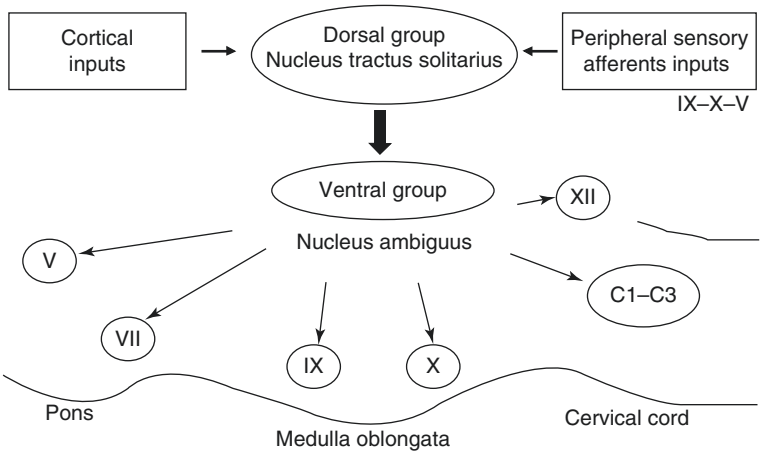

Fig. 8.2 Schematic representation of the central pattern generator (CPG). Sensory inputs from the periphery (oral cavity, pharynx, and larynx) and cortical afferents project around the nucleus of the solitary tract (dorsal swallowing group). The dorsal group integrates these informations, develops the motor swallowing program, and transmits this program to the premotor neurons of the ventral group, located next to the nucleus ambiguus (Adapted from [6, 7])

The sensory inputs come primarily from the glossopharyngeal nerve (IX) and the superior laryngeal nerve, a branch of the vagus nerve (X). Both are crucial for airway protection. Stimulation of areas innervated by the glossopharyngeal nerve appears to facilitate swallowing in humans [8]. Superior laryngeal nerve stimulation is also efficient to trigger swallowing in most mammals [9]. Informations from the glossopharyngeal and superior laryngeal nerves are transmitted to the swallowing center via the solitary tract. To the sensory inputs coming from the superior laryngeal and glossopharyngeal nerves must be added the influence of sensory afferents from the trigeminal nerve (V) and, particularly from one of its branches, the mandibular nerve (V3). Mechanoreceptors located in the oral cavity and at the level of the temporomandibular joints provide informations on the consistency and volume of the bolus. They modulate the motor response by changing its amplitude and/or duration.

Located in the brain stem, the medulla oblongata contains a network of interneurons responsible for the development of the swallowing motor program [6]. This network is divided into two groups: a dorsal group, organized at the level of the dorsal solitary nucleus and reticular formation, and a ventral group, organized around the nucleus ambiguus. The former receives both sensory inputs from the periphery and cortical afferents. It develops the motor program transmitted to the swallowing motor nuclei by the ventral cluster. The trigeminal motor nuclei are located in the middle part of the pons. They innervate the tensor veli palatini, the anterior belly of digastric, mylohyoid muscles, masseter muscles, temporalis muscles, and medial and lateral pterygoid muscles. The facial motor nuclei are located at the bottom of the pons. They control the muscles of facial expression, the posterior belly of digastric, and stylohyoid muscles. The nucleus ambiguus, which occupies the entire height of the medulla oblongata, controls the innervation of the esophagus and the velopharynx (motor fibers of IX and X) via its rostral part, whereas its caudal part innervates the larynx (the bulbar accessory nerve [XI]). The hypoglossal nuclei (XII) associated with the C1 roots innervate the muscles of the tongue. The C2 and C3 cervical roots, together with the hypoglossal nerves, control the infrahyoid muscles.

In summary, sensory informations are dependent on three pairs of cranial nerves: the trigeminal (V), the glossopharyngeal (IX), and the vagus nerves (X). Yet, afferents from the superior laryngeal nerve (a branch of the X) are the most powerful to trigger swallowing. The innervation of the different muscles involved in swallowing is, in turn, provided by five pairs of cranial nerves: the trigeminal (V), the facial (VII), the glossopharyngeal (IX), the vagus (X), and the hypoglossal nerves (XII) (Table 8.1).

Table 8.1 Cranial nerves involved in the process of swallowing

Cranial nerves	Role
V Trigeminal	Sensory: face, mouth, cheek, chin, lips, palate, teeth, nasal cavity, mandible, anterior two-thirds of the tongue
Three branches	
Ophthalmic nerve (V1)	Motor: masticator muscles, tensors of the soft palate, mylohyoid muscles, anterior belly of digastric
Maxillary nerve (V2)	
Mandibular nerve (V3)	
VII Facial	Taste: two-thirds of the tongue
	Secretory: lacrimal, submandibular, and sublingual glands, mucous membranes of the palate and nose
	Motor: facial expression muscles, nasal muscles, posterior belly of digastric, stylohyoid muscles, stapedius muscles
IX Glossopharyngeal	Taste: posterior third of the tongue
	Secretory: parotid glands
	Sensory: posterior third of the tongue, pharynx, and soft palate
	Motor: stylopharyngeus muscle, pharyngeal constrictors
X Vagus	Taste: epiglottic region and root of the tongue
	Sensory: epiglottis, laryngeal mucosa
	Motor: esophageal muscles, laryngeal muscles (except stylopharyngeus) with the help of the accessory nerve (XI), muscles of the soft palate (except tensor veli palatini)
XII Hypoglossal	Motor: all the muscles of the tongue (except palatoglossus), geniohyoid muscles, thyrohyoid muscles

Adapted from [5, 10, 11]

Swallowing and Consciousness

Animal Studies

At the beginning of the last century, Sherrington studied swallowing in decerebrate cats (cats with brain regions located above the pons disconnected from the brain stem) [12]. He observed that stimulation of the superior laryngeal nerve using various stimuli (electrical, mechanical, liquid, or chemical) could trigger swallowing. This swallowing movement, neither involving oral preparation nor propulsion of the bolus, was defined as reflex. Swallowing reflex was also observed in decerebrate and anesthetized goats. It was triggered by electrical stimulation of the superior laryngeal nerve [13]. When trying to reproduce the experiment with an electrical stimulation of the glossopharyngeal nerve, no swallowing reflex could be observed. However, stimulation of the glossopharyngeal nerve seems to facilitate the swallowing movements induced by stimulation of the superior laryngeal nerve. These experiments suggest that swallowing movements in decerebrate mammals is possible and that cortical control is not essential.

Human Studies

Ultrasound studies on oral sensorimotor function and swallowing in human fetuses show early onset of swallowing mechanisms [14]. Indeed, the swallowing is important for the regulation of the volume and composition of the amniotic fluid. The pharyngeal phase of swallowing is one of the first pharyngeal motor responses observed in fetuses and appears between the 10th and 14th week of gestation. In the brain stem, the network of interneurons in charge of the control of the pharyngeal phase of swallowing achieved a functional level during fetal development as early as the 11th week. From the 22nd to 24th weeks of gestation, swallowing movements are constantly observed. Even in the absence of cortex in the human fetus, the swallowing reflex can be observed. Indeed, several ultrasound studies show the presence of swallowing movements in anencephalic fetuses [15]. Therefore, in human, swallowing movements can be achieved even before the complete development of cortical and subcortical structures. On the other hand, many electrophysiological, neuroimaging, and clinical observations show that the cerebral cortex plays an important role in the process of swallowing [16–18], even when the swallowing is considered as reflex or automatic [19, 20]. Cortical involvement is particularly evident when looking at the incidence of dysphagia among subjects suffering from stroke. In these patients, with anoxic brain damage, the rate of dysphagia ranges from less than 30% [21] to more than 50% [22]. Since the early studies of cortical electrical stimulation done by Penfield, the involvement of the cerebral cortex in the process of swallowing has been refined. Through the use of transcranial magnetic stimulation (TMS), Hamdy and colleagues demonstrated the existence of an asymmetrical somatotopic representation of the muscles involved in swallowing, not correlated to the subject's handedness [23]. Following stroke, damage of the hemisphere with the largest representation of the corticospinal tract involved in swallowing increases the risk of dysphagia [23]. And in case of unilateral involvement of the corticospinal tract, recovery of an effective swallowing function depends on the presence and development of the same tract in the contralateral hemisphere [24–26]. Development of functional imaging techniques (positron emission tomography (PET) and functional magnetic resonance imaging (fMRI)) has revolutionized the study of the cortical mechanisms involved in swallowing. They confirm the important role of the cerebral cortex. According to these neuroimaging studies, the main cortical and subcortical areas involved in swallowing are the cerebellum, the basal ganglia, and the sensorimotor, prefrontal, anterior cingulate, insula, and temporoparietal regions [27–31].

Precentral Gyrus

The precentral gyrus is the most consistently cited region in functional imaging studies exploring swallowing. It encompasses the premotor cortex (including the

supplementary motor area, SMA) and the primary motor cortex. This region controls the muscles of the oral cavity, pharynx, and larynx [23] and is mainly involved in planned and voluntary movements. The precentral gyrus also seems active during the production of automatic swallowing, and its role in the execution of automatic movement has to be clarified [19]. The SMA is located in front of the primary motor cortex. This region is related to the planning of complex movements and especially sequential movements. The SMA has a modulatory action on the motor sequence and is involved in the initiation of the pharyngoesophageal phase of swallowing [27].

The Prefrontal Cortex

The prefrontal cortex is the anterior part of the frontal lobe and is located in front of the premotor areas. This region is associated with the planning of complex cognitive tasks. It is involved in the genesis of emotional states and in the regulation of autonomic changes accompanying those states. The prefrontal cortex is also implicated in the analysis of olfactory information.

The Anterior Cingulate Cortex

The anterior cingulate cortex is important for conscious awareness and for the processing of stimuli related to emotion. Activation of the anterior cingulate cortex could account for the affective and attentional aspect of swallowing. Others consider this region (which is involved in cognitive and attentional processes) as an interface between intention and execution of the motor sequences involved in swallowing [32]. In addition, the anterior cingulate cortex also plays a role in mediating the visceral motor responses of the digestive tract.

The Insula

Several functional neuroimaging studies report activation of the insula during swallowing [19, 27, 33]. Damage to this isolated region may induce dysphagia [33]. The insula is involved, among other regions, in monitoring and analyzing informations concerning the body's homeostatic state. It is also involved in visceral motor control (automatic) [34], somatic sensations of the orofacial region in primates, voluntary control of orofacial movements, and control of speech. Activation of the insula seems to play a role in integrating the sensory and motor aspects of the digestive tract.

Parietal Regions and the Postcentral Gyrus

The sensory cortex is involved in the processing of facial as well as gustatory stimuli [35]. Its activation during swallowing reflects the large number of sensory informations coming from the oropharyngeal region. As already discussed, the sensory inputs are essential for the regulation of swallowing [19].

Temporal Regions

In their work, Martin and colleagues proposed to link the temporal cortex activation, more exactly the primary auditory cortex, to the analysis of acoustic stimuli produced by chewing and swallowing [19]. Indeed, we receive, via bone conduction, sounds associated with swallowing. Furthermore, a PET study suggested the involvement of the anteromedial portion of the temporal lobe in the recognition of gustatory stimuli [36].

The Basal Ganglia

The basal ganglia encompass several subcortical structures such as the caudate nucleus, putamen, or globus pallidus. These structures receive information from various brain areas (frontal, prefrontal, and parietal) and transmit them to the SMA. In doing so, the basal ganglia exert a facilitator effect on movement. Clinical studies show that lesions of the basal ganglia, as found in Parkinson's disease, lead to difficulties in coordinating the oropharyngeal phase of swallowing.

The Cerebellum

The cerebellum is known to be a regulator of the motor sequence [37–39]. It integrates the sensory inputs and organizes, based on these inputs, the efferent motor response [40]. It ensures a correct pharyngeal and laryngeal synergy and chronometry such as elevating the larynx, closing the glottis, or triggering the swallowing reflex.

Most studies are based on observation of the mechanisms involved during voluntary swallowing (i.e., the swallowing of food or saliva on command); therefore, it is not surprising that many different cortical areas are implicated. But cortical control is also observed during reflex swallowing [19, 20]. Swallowing apraxia—characterized by the inability to perform reflex swallowing while voluntary swallowing (i.e., swallowing on command) is preserved—was observed in some patients with left frontolateral cortical lesions [41]. The network of brain regions activated during reflex swallowing is different from that observed during voluntary swallowing. According to Kern et al., reflex swallowing only activates the primary sensorimotor

cortex in contrast to voluntary swallowing which activates, in addition to this region, a multitude of other cortical regions such as the insula, prefrontal and cingulate gyri, cuneus, and precuneus [20]. These additional regions could reflect the preparation and the voluntary realization of the movement. Another study of Martin and colleagues showed a higher activity of the posterior region of the anterior cingulate gyrus during voluntary swallowing as opposed to reflex swallowing [19]. Thus, studies in human adults show that a certain level of cortical integrity is necessary both for voluntary and reflex swallowing. However, the impact of the level of consciousness on a patient's swallowing ability has to be determined. The observation of swallowing in different physiological alteration of consciousness (e.g., during sleep) or under medication (e.g., during anesthesia) gives us some insights. During sleep, swallowing movements are less frequent, and long periods with no swallowing movement are observed. When swallowing occurs, it is associated with signs of awakenings on electroencephalography (EEG), both during REM (rapid eye movement) and non-REM sleeps. Moreover, the frequency of swallowing movements seems related to the stage of sleep. When sleep deepens, they are less frequent [42, 43]. Changes in swallowing reflex are often observed during the perioperative period. Several reasons can explain this alteration: traumatic reasons (i.e., mucosal lesions as a consequence of endotracheal intubation) and pharmacological reasons associated to the own pharmacodynamic effects of each anesthetic agent used, including alteration of consciousness [44].

Oral Feeding in Patients with Disorder of Consciousness

Over the past 15 years, the scientific community has developed a growing interest toward swallowing disorders in severe brain-injured patients. Swallowing disorders associated with traumatic or anoxic brain injury is frequent (between 25 and 61%) [1–3], and repeated inhalation can lead to complications (e.g., aspiration pneumonia) with dramatic consequences in this fragile population. It is therefore essential to assess swallowing in order to avoid medical complication and reduce the duration of hospitalization in acute patient. However, few studies specifically focused on the prognostic value of dysphagia on recovery as well as on the rehabilitation methods that could be implemented for severe brain-injured patients. Indeed, the fluctuation of consciousness, the severe cognitive dysfunction, and the communication difficulty make the standard swallowing assessment quite challenging in this specific population. Moreover, in an acute setting, the neurologic evaluation and the preservation of vital functions are often considered as priority.

Nowadays, although most patients recover from coma within the first days after a traumatic or anoxic brain injury, some progress through different stages (vegetative state or unresponsive wakefulness syndrome (UWS), minimally conscious state (MCS), or locked-in syndrome) before fully or partly recovering consciousness. UWS patients are awake but lack awareness. The brain stem functions of UWS patients are preserved, while the cortical white and gray matters are severely

affected. They are able to perform a variety of reflexive movements but have a major impairment of their associative cortices involved in the realization of complex information processing such as memory, attention, planning, or language. Unlike UWS patients, MCS patients show reproducible but fluctuating signs of consciousness (e.g., visual tracking or response to command). MCS patients are, however, not able to communicate [45]. Their brain metabolic activity is higher than in UWS patients [46], and their (brain association areas) are less affected.

Several studies focused on the recovery of a safe functional swallowing function in severe brain-injured patients. In a prospective study done by MacKay and colleagues, 61% of patients with traumatic brain injury have swallowing disorder, and 41% show signs of aspiration [1]. The severity of the swallowing disorders is related to a low score on the *Glasgow Coma Scale* (*GCS*), a low *Ranchos Los Amigos* (RLA) score [57], the presence of a tracheotomy, and at least 2 weeks of mechanical ventilation. The authors concluded that cognitive levels not only affect the moment patients start to eat but also their ability to tolerate a full oral diet. Similarly, Ward and colleagues observed that patients with a GCS score between 3 and 8 showed a longer delay before the resumption of oral feeding compared to patients with a GCS score above 8 [58]. They also claimed that the faster the evaluation of the swallowing function and the initiation of swallowing rehabilitation, the faster the recovery of a full oral diet. A retrospective study looked at the frequency of swallowing dysfunction in a population of patients with traumatic head injury [2]. Twenty-seven percent of the 201 patients (55/201) had swallowing dysfunction. Of those, 82% (45/55) could not achieve a safe oral feeding, and the majority of those 45 patients had a severe disorder of consciousness (UWS or MCS). The authors concluded that in order to achieve oral feeding, patients need to have a good cognitive control. Recently, a restrospective study looked at the correlation between the diagnostic at the admission and oral feeding recovery in traumatic brain-injured patients [48]. Overall, 93% of the patients included had swallowing dysfunction at the admission, and 64% could achieve oral feeding at the end of the rehabilitation period. Achieving oral feeding was clearly correlated to the level of consciousness on admission. Twenty-four percent of the coma or UWS subjects (RLA I or II), 77% of the MCS (RLA III), and 88% of the exit MCS (RLA IV or V) could achieve oral feeding by the end of the rehabilitation period. In a restrospective study done by Formisano and colleagues [56] the shorter the time between the traumatic brain injury and the recovery of an oral feeding, the better the recovery on a consciousness level. Other studies also show that low level of consciousness is associated with low oral feeding capacity [49, 50].

Some studies focus on the feasibility of an effective swallowing assessment and rehabilitation in patients with severe disorders of consciousness. Pirozzi and colleagues evaluated 12 tracheotomized patients with severe disorder of consciousness following a traumatic brain injury [51]. One of the secondary objectives of the study was the feasibility of using liquid or solid food in a sensory stimulation program at the acute phase. Of the 12 subjects, 7 were diagnosed as UWS (RLA score of II) and 5 as MCS (RLA score of III). For 92% of the patients, a comprehensive swallowing assessment including video fluoroscopy (using four substances of different consis-

tencies) could be achieved. Video fluoroscopy involves the ingestion of a barium-based contrast. The progression and distribution of this product in the oral cavity, pharynx, and esophagus are then followed using an X-ray system, allowing the observation and evaluation of the three phases of swallowing. Thus, according to this study, it seems possible to objectively assess the patient's swallowing abilities regardless of the level of consciousness. It should be noted that the authors have reported signs of aspiration in 25% of their subjects ($n = 3$), which is less than the aspiration rate reported by MacKay and colleagues [1]. In these three patients, two were UWS and had lesions in the brain stem and cortex. The third was MCS and had only cortical lesions. The aspirations observed in these three patients were silent (i.e., occurring without visible or audible sign such as a cough reflex). This corroborates previous publications showing that traditional clinical bedside swallowing assessments are only 66% accurate in screening aspiration risks [52, 53]. Therefore, making a decision on whether oral feeding can be safely resumed cannot be done based on bedside evaluation alone. Besides swallowing assessment, the authors performed various rehabilitation exercises with the patients [51]. Their oral feeding rehabilitation program included motion exercises, thermal stimulations, the use of small amounts of specified food and/or liquid with various consistencies, therapy to reduce bite reflex, and caregiver education. Following this therapy, none of the patients developed aspiration pneumonia. When discharged from the acute care, all subjects could ingest some amount of food and/or drink. Moreover, gastrostomy could be withdrawn in five subjects since oral feeding was sufficient to meet their daily needs. An improvement in cognitive behavioral functions was also observed in 10 of the 12 subjects (6 UWS and 4 MCS). They had an RLA score of III–VII at the time of discharge. Again, the patient's swallowing abilities seem to be related to changes in the patient's level of consciousness, at least during the acute phase. However, it is impossible to determine whether the increase of oral feeding is related to the rehabilitation effect or to the spontaneous evolution of consciousness. Brady and colleagues [4] evaluated 25 patients with altered state of consciousness with an RLA score varying between II and III (UWS and MCS). These patients were divided into two groups: one group of 10 subjects, with a RLA score of III, rapidly received oral feeding, and a second group of 15 subjects had a delayed initiation of oral feeding. In this second group, oral feeding was initiated as soon as an RLA score of III or more was reached. For all these patients, an objective swallowing assessment was performed either by video fluoroscopy or fiber-optic endoscopic evaluation. None of the patient showed evidence of inhalation during the evaluation. None of the patient with an RLA score lower than III received oral feeding. At discharge, when considering the number of patients receiving three oral meals a day, there was no difference between the two groups. Again, this study highlights the fact that objective swallowing assessments can be performed in patients with an altered state of consciousness. The study showed that oral feeding is related to consciousness. On the contrary, there seems to be no relationship between early therapeutic oral feeding and improvement of consciousness. The authors concluded that providing therapeutic oral feeding (i.e., small amounts of food given by a speech therapist) to patients with an RLA score of III (MCS) under specific conditions is safe. These

conditions are no demonstration of aspiration or elimination of aspiration by means of volume or consistency modification (on a baseline instrumental swallowing examination) and close supervision during oral feeding. Recently, there has been an interest in the utilization of the facial oral tract therapy (FOTT) as an assessment and rehabilitation tool for patients with disorders of consciousness. The FOTT is a multidisciplinary approach to the evaluation and rehabilitation of swallowing, oral hygiene, and in neurological patients [54]. This method seems particularly suitable for patients with disorders of consciousness since the FOTT does not need the patient to understand the instructions or to respond to command. An adaptation of the FOTT to disorders of consciousness patients was recently published [55], and future studies are needed to evaluate the efficacy of this method in these patients.

Conclusions

Swallowing is a complex sensorimotor function divided into three phases: oral, pharyngeal, and esophageal. The achievement of the complete swallowing sequence involves the muscles of the face, tongue, pharynx, larynx, and esophagus, with a total of 26 pairs of muscles plus the unique superior longitudinal lingual muscle and five pairs of cranial nerves. Various regions of the central nervous system, from brain stem to cortex, are involved in the realization of this complex sensorimotor sequence. Because the respiratory and digestive tracts cross in the pharynx, the slightest misstep in the sequence of swallowing may lead to complications, sometimes life threatening. The study of the neurophysiology of swallowing has evolved since the late nineteenth century and Penfield's studies, using direct electrical brain stimulation, to the most recent studies using TMS, PET, and fMRI. Initially, researches focused on the study of peripheral nerves, the organization of the CPG, and the importance of the brain stem. Later, they focused on the involvement of cortical and subcortical regions in reflex and voluntary swallowing movements and the interactions between cortical regions and the CPG.

Dysphagia concerns more than half of the patients with severe brain injury [1] and only a few UWS and MCS patients receive oral feeding. We know that swallowing is controlled by a region located in the brain stem, the CPG, which incorporates the afferents coming from the periphery in order to select the best motor response. We also know that for both voluntary and reflex swallowing, cortical and subcortical brain structures are involved. Only a few studies focused on swallowing disorders in patients with impaired consciousness. All tend to claim that the level of consciousness during the acute phase determines the feasibility of resuming oral feeding [1, 2, 4, 47–51, 56]. Similarly, rapid resumption of oral feeding in patients with altered state of consciousness is considered as a sign of better prognosis [56]. This is true in the acute phase, and it would be interesting to evaluate whether a relationship between consciousness and oral feeding still exists in the chronic phase. Conversely, the use of therapeutic oral feeding does not appear to affect the recovery of consciousness [4]. Thus, rehabilitation of swallowing should not be considered as a

therapeutic tool but rather as a management option for these patients. Rehabilitation of swallowing, as part of a more global sensory stimulation program, could be achieved in this particular population and improve patient's quality of life. Indeed, administration of a therapeutic oral feeding in selected patients (with RLA score III [MCS]) is safe [4]. Recently, the FOTT has been suggested as an interesting rehabilitation method for this specific population of patients [55]. Because of the limited number of studies that has addressed this issue and because those studies included small amount of patients, it is difficult to give a clear and definitive answer to our initial questions. Further studies have to be performed in larger sample of patients and have to evaluate the relationship between consciousness recovery, lesions of the central nervous system, and swallowing abilities, both during acute and chronic phase. They should also evaluate the benefits of swallowing rehabilitation in terms of quality of life and functional recovery.

In conclusion, the evaluation of swallowing abilities is important and should be a part of the evaluation of all patients with altered state of consciousness. Indeed, whatever the underlying neurological disease, dysphagia, because of its potential respiratory and nutritional complications, is a marker of poor prognosis.

References

1. Mackay LE, Morgan AS, Bernstein BA. Factors affecting oral feeding with severe traumatic brain injury. J Head Trauma Rehabil. 1999;14:435–47.
2. Winstein CJ. Neurogenic dysphagia. Frequency, progression, and outcome in adults following head injury. Phys Ther. 1983;63(12):1992–7.
3. Mackay LE, Morgan AS, Bernstein BA. Swallowing disorders in severe brain injury: risk factors affecting return to oral intake. Arch Phys Med Rehabil. 1999;80:365–71.
4. Brady SL, Darragh M, Escobar NG, et al. Persons with disorders of consciousness: are oral feedings safe/effective? Brain Inj. 2006;20:1329–34.
5. Bleeckx D. Dysphagie: évaluation et rééducation des troubles de la déglutition. 1st ed. Brussels: De Boeck; 2002.
6. Jean A. Brain stem control of swallowing: neuronal network and cellular mechanisms. Physiol Rev. 2001;81:929–69.
7. Ertekin C, Aydogdu I. Neurophysiology of swallowing. Clin Neurophysiol. 2003; 114:2226–44.
8. Sinclair WJ. Initiation of reflex swallowing from the naso- and oropharynx. Am J Physiol. 1970;218:956–60.
9. Doty R. Neural organisation of deglutition. In: Code CF, editor. Handbook of physiology. Washington: American Physiological Society; 1968. p. 1861–902.
10. McFarland. L'anatomie en orthophonie : Parole, voix et déglutition. Elsevier Masson; 2006.
11. Mistry S, Hamdy S. Neural control of feeding and swallowing. Phys Med Rehabil Clin N Am. 2008;19:709–28, vii–viii.
12. Miller FR, Sherrington CS. Some observations on the buccopharyngeal stage of reflex deglutition in the cat. Q J Exp Physiol. 1916;9:147–86.
13. Ciampini G, Jean A. Role of glossopharyngeal and trigeminal afferents in the initiation and propagation of swallowing. I–Glossopharyngeal afferents. J Physiol Paris. 1980;76:49–60.
14. Delaney AL, Arvedson JC. Development of swallowing and feeding: prenatal through first year of life. Dev Disabil Res Rev. 2008;14:105–17.

15. Peleg D, Goldman JA. Fetal deglutition: a study of the anencephalic fetus. Eur J Obstet Gynecol Reprod Biol. 1978;8:133–6.
16. Martin RE, Sessle BJ. The role of the cerebral cortex in swallowing. Dysphagia. 1993;8:195–202.
17. Miller AJ. The neuroscientific principles of swallowing and dysphagia. San Diego: Singular Publication Group; 1999.
18. Michou E, Hamdy S. Cortical input in control of swallowing. Curr Opin Otolaryngol Head Neck Surg. 2009;17:166–71.
19. Martin RE, Goodyear BG, Gati JS, Menon RS. Cerebral cortical representation of automatic and volitional swallowing in humans. J Neurophysiol. 2001;85:938–50.
20. Kern MK, Jaradeh S, Arndorfer RC, Shaker R. Cerebral cortical representation of reflexive and volitional swallowing in humans. Am J Physiol Gastrointest Liver Physiol. 2001;280:G354–60.
21. Young EC, Durant-Jones L. Developing a dysphagia program in an acute care hospital: a needs assessment. Dysphagia. 1990;5:159–65.
22. Gordon C, Hewer RL, Wade DT. Dysphagia in acute stroke. Br Med J (Clin Res Ed). 1987;295:411–4.
23. Hamdy S, Aziz Q, Rothwell JC, et al. The cortical topography of human swallowing musculature in health and disease. Nat Med. 1996;2:1217–24.
24. Hamdy S, Aziz Q, Rothwell JC, et al. Explaining oropharyngeal dysphagia after unilateral hemispheric stroke. Lancet. 1997;350:686–92.
25. Hamdy S, Rothwell JC, Aziz Q, et al. Long-term reorganization of human motor cortex driven by short-term sensory stimulation. Nat Neurosci. 1998;1:64–8.
26. Hamdy S, Aziz Q, Rothwell JC, et al. Recovery of swallowing after dysphagic stroke relates to functional reorganization in the intact motor cortex. Gastroenterology. 1998;115:1104–12.
27. Hamdy S, Mikulis DJ, Crawley A, et al. Cortical activation during human volitional swallowing: an event-related fMRI study. Am J Physiol. 1999;277:G219–25.
28. Hamdy S, Rothwell JC, Brooks DJ, et al. Identification of the cerebral loci processing human swallowing with H2(15)O PET activation. J Neurophysiol. 1999;81:1917–26.
29. Mosier K, Patel R, Liu WC, et al. Cortical representation of swallowing in normal adults: functional implications. Laryngoscope. 1999;109:1417–23.
30. Zald DH, Pardo JV. The functional neuroanatomy of voluntary swallowing. Ann Neurol. 1999;46:281–6.
31. Mosier KM, Liu WC, Maldjian JA, Shah R, Modi B. Lateralization of cortical function in swallowing: a functional MR imaging study. AJNR Am J Neuroradiol. 1999;20:1520–6.
32. Paus T. Primate anterior cingulate cortex: where motor control, drive and cognition interface. Nat Rev Neurosci. 2001;2:417–24.
33. Daniels SK, Foundas AL. The role of the insular cortex in dysphagia. Dysphagia. 1997;12:146–56.
34. Penfield W, Rasmussen T. The cerebral cortex of man. New York: Macmillan; 1950.
35. Burton H, Benjamin RM. Central projections of the gustatory system. In: Beidler LM, editor. Handbook of sensory physiology. Chemical senses Sect 2, taste, vol 4. Berlin: Springer; 1971. p. 148–63.
36. Small DM, Jones-Gotman M, Zatorre RJ, et al. A role for the right anterior temporal lobe in taste quality recognition. J Neurosci. 1997;17:5136–42.
37. Miall RC. The cerebellum, predictive control and motor coordination. Novartis Found Symp. 1998;218:272–84; discussion 84–90
38. Ivry R. Cerebellar timing systems. Int Rev Neurobiol. 1997;41:555–73.
39. Doya K. Complementary roles of basal ganglia and cerebellum in learning and motor control. Curr Opin Neurobiol. 2000;10:732–9.
40. Hikosaka O, Nakahara H, Rand MK, et al. Parallel neural networks for learning sequential procedures. Trends Neurosci. 1999;22:464–71.
41. Robbins J, Levin RL. Swallowing after unilateral stroke of the cerebral cortex: preliminary experience. Dysphagia. 1988;3:11–7.

42. Lichter I, Muir RC. The pattern of swallowing during sleep. Electroencephalogr Clin Neurophysiol. 1975;38:427–32.
43. Sato K, Nakashima T. Human adult deglutition during sleep. Ann Otol Rhinol Laryngol. 2006;115:334–9.
44. de Larminat V, Dureuil B. Changes in the deglutition reflex during the perioperative period. Ann Fr Anesth Reanim. 1994;13:49–56.
45. Giacino JT, Ashwal S, Childs N, et al. The minimally conscious state: definition and diagnostic criteria. Neurology. 2002;58:349–53.
46. Laureys S, Owen AM, Schiff ND. Brain function in coma, vegetative state, and related disorders. Lancet Neurol. 2004;3:537–46.
47. MacKay LaM AS. Early swallowing disorders with severe head injuries: relationships between the RLA and the progression of oral intake. Dysphagia. 1993;8:161.
48. Hansen TS, Engberg AW, Larsen K. Functional oral intake and time to reach unrestricted dieting for patients with traumatic brain injury. Arch Phys Med Rehabil. 2008;89(8): 1556–62.
49. Cherney LR, Halper AS. Swallowing problems in adults with traumatic brain injury. Semin Neurol. 1996;16:349–53.
50. Morgan A, Ward E, Murdoch B, et al. Incidence, characteristics, and predictive factors for Dysphagia after pediatric traumatic brain injury. J Head Trauma Rehabil. 2003;18:239–51.
51. O'Neil-Pirozzi TM, Momose KJ, Mello J, et al. Feasibility of swallowing interventions for tracheostomized individuals with severely disordered consciousness following traumatic brain injury. Brain Inj. 2003;17:389–99.
52. Splaingard ML, Hutchins B, Sulton LD, Chaudhuri G. Aspiration in rehabilitation patients: video fluoroscopy vs bedside clinical assessment. Arch Phys Med Rehabil. 1988;69:637–40.
53. Linden P, Kuhlemeier KV, Patterson C. The probability of correctly predicting subglottic penetration from clinical observations. Dysphagia. 1993;8:170–9.
54. Coombes K. FOTT (facial oral tract therapy). iADH Magazine. International Association for Disability and Oral Health; 2008; 11-2, http://iadh.org/wp-content/uploads/2014/01/2008spring.pdf
55. Bicego A, Lejoly K, Maudoux A, et al. Déglutition et états de conscience altérée (Swallowing in disorders of consciousness). Rev Neurol (Paris). 2014;170(10):630–41.
56. Formisano R, Voogt RD, Buzzi MG, et al. Time interval of oral feeding recovery as a prognostic factor in severe traumatic brain injury. Brain Inj. 2004;18:103–9.
57. Hagen C. The Rancho levels of cognitive functioning. The revised levels. 3rd ed. Downey: Rancho Los Amigos Medical Center; 1998.
58. Ward EC, Green K, Morton AL. Patterns and predictors of swallowing resolution following adult traumatic brain injury. J Head Trauma Rehabil. 2007;22(3):184–91.

Chapter 9
What Can We Learn About Brain Functions from Sleep EEG? Insights from Sleep of DOC Patients

Malgorzata Wislowska and Manuel Schabus

Abstract Disorder of Consciousness (DOC) patients are often reported to have alterations in sleep architecture and sleep-specific graphoelements. The reappearance of non-REM oscillatory patterns such as sleep spindles has been associated with diagnosis and presumably prognosis.

The study of sleep is of particular interest in DOC research as it might allow identifying lesioned neuronal tissue linked to specific sleep graphoelements. The presence of REM, for example, may reflect residual functioning of brainstem nuclei including pons and adjacent portions of the midbrain. On the other hand, the absence of circadian functioning, or sleep-wake cycles, has been associated with brainstem dysfunction and might be informative for hypothalamic and SCN alterations. Interestingly, the systematic work on sleep and circadian functioning in the various DOC states is still scarce. Most strikingly, there are no accepted criteria which allow to reliably classify sleep stages in these patients. In addition, there is very little knowledge whether sleep in DOC is still under normal circadian and homeostatic control. Without a doubt, studying sleep in DOC is a challenging endeavor, and long-term polysomnography (PSG) of DOC patients is difficult for many reasons, among which are ubiquitous artifacts present in the data recordings or PSG alterations which often come with pharmacological treatment.

Altogether, the characterization of sleep and its relationships with arousal, homeostasis, and circadian rhythmicity is, in our view, essential in order to better understand the various DOC states and might offer complementary diagnostic and prognostic information or even guide the direction of future treatment attempts.

M. Wislowska • M. Schabus, Ph.D. (✉)
Laboratory for Sleep, Cognition and Consciousness Research, Department of Psychology, University of Salzburg, Hellbrunnerstr. 34, 5020 Salzburg, Austria

Centre for Cognitive Neuroscience Salzburg (CCNS), Salzburg, Austria
e-mail: manuel.schabus@sbg.ac.at

C. Schnakers, S. Laureys (eds.), *Coma and Disorders of Consciousness*,
DOI 10.1007/978-3-319-55964-3_9

States of Reduced Consciousness

Nowadays consciousness is considered to consist of two major components: arousal and awareness. Arousal refers to the level of consciousness (i.e., vigilance) and is supported by brainstem neuronal populations projecting to both thalamic and cortical areas. Awareness on the other hand refers to the content of consciousness (i.e., awareness of the self and of the environment) and relies on the functional integrity of the cerebral cortex and its subcortical connections. Both components can be considered representing a continuum.

In every healthy individual, the level of consciousness (both on the arousal and awareness scale) varies in a cycling manner over 24-h periods. When falling asleep consciousness progressively decreases from wake to non-rapid eye movement (NREM) sleep stage N1 (a transitory sleep state), to light sleep stage N2 and deep sleep N3. Changes in the level of consciousness are not only reflected behaviorally but can also be observed in changing brain activity patterns measured with electroencephalography (EEG) and accompanied by changes in muscle and eye activity. This method including brain activity, muscle, eye and usually heart and respiration signals is usually referred to as polysomnography (PSG).

In some situations however, one or both components of consciousness are altered in a pathological way. This, for instance, can be observed in patients, who survived a severe brain injury and which progress through different stages of disorders of consciousness (DOC), i.e., coma, unresponsive wakefulness state (UWS), or minimally conscious state (MCS). The biggest determinant for later recovery and prognosis of DOC patients is the etiology of the disorder with non-traumatic hypoxia being related to poor prognosis and traumatic brain injury being related to better prognosis. It has to be noted that most older studies might have mixed the two clinical entities UWS and MCS, since the MCS entity was only introduced in 2002 by Giacino [1].

Brain injury survivors initially fall into a state of coma, which is characterized by no signs of awareness or arousal and a lack of responses to stimulation. If patients do not permanently lose all brain (i.e., brain death) or motor (i.e., locked-in syndrome, LIS) functions, they typically progress within the first days or weeks into UWS and/or MCS. In general, coma is considered as deregulation of the brain's arousal system resulting from diffuse brain damage or from brainstem lesions.

The most typical EEG patterns observed in coma are prevalent alpha oscillations or so-called alpha coma (AC), abundant spindle-like activity called spindle coma (SC), or triphasic waves [2]. In AC, alpha activity between 8 and 12 Hz is dominating the frequency spectrum and presents a usual widespread topography with often high amplitudes at frontal electrodes. No posterior block of alpha oscillations can be observed in response to eye opening. AC patterns have been described after hypoxia as well as drug intoxications. SC is an EEG pattern in the 9–14 Hz range present on the background of slow delta (0.9–4 Hz) and theta (4–8 Hz) activity. SC however has been observed only in a minority of patients [3]. Triphasic waves consist in

bursts of moderate to high amplitude (100–300 μV) activity, usually of 1.5–2.5 Hz, and frequently predominating in frontal regions. The initial negative component is the sharpest, whereas the following positive portion of the complex is the largest and is followed by another negative wave. Triphasic waves are usually bisynchronous but may show shifting asymmetries. Persistent asymmetry suggests an underlying structural lesion on the side of the lower amplitude.

Unlike coma patients, UWS patients open and close their eyes (i.e., revive arousal) and thereby exhibit—at least at a behavioral level—a state which resembles normal sleep-wake cycling. Patients in UWS are unresponsive to external stimuli and are considered to be completely unaware. This entity involves a total loss of forebrain, but a preservation of brainstem functions (i.e., breathing, swallowing, or cranial nerve reflexes) [4].

In EEG, they occasionally exhibit electro-cerebral inactivity (i.e., no cerebral activity over 2 μV), although the majority shows EEG activity with pronounced slowing and a lack of a clear alpha peak.

Once a patient presents inconsistent but clearly discernible signs of awareness, he/she is diagnosed as MCS. Since the spectrum of recovered awareness is rather broad and embraces simple behaviors such as sustained visual pursuit up to complex functions such as intentional (yet inconsistent) communication, it has been proposed to further divide this clinical entity into the subcategories MCS− and MCS+, respectively [5].

Patients with preserved consciousness, but no motor functions (i.e., LIS patients), are often clinically misdiagnosed to be unaware. Brain lesions in these LIS patients affect the ventropontine area sparing the pontine tegmentum. A concomitant cerebellum lesion is frequent as there is a rupture of the basilar artery. LIS patients are strictly speaking not suffering from a DOC, yet based on their behavior they are often confused to be in UWS or even coma.

Sleep

Circadian variation of human rhythms is endogenously controlled by a biological "zeitgeber" located in the hypothalamic suprachiasmatic nucleus (SCN). On the behavioral level, the most prominent circadian cycling can be observed in the arousal level—i.e., the sleep-wake rhythm—which is accompanied by variation of blood pressure, heart rate, hormone secretion, or body temperature.

PSG, which is the only valid sleep recording method, can be used to perform a clinical assessment of day-night variations or arousal as well as sleep architecture. From a physiological point of view, normal sleep is associated with well-described cycles, stages, arousals, and microstructures (see Fig. 9.1). Yet the current state-of-the-art scoring manual from the American Academy of Sleep Research (AASM; [6]) was not designed for clinical contexts and therefore lacks specifications when it comes to severely altered sleep such as in DOC.

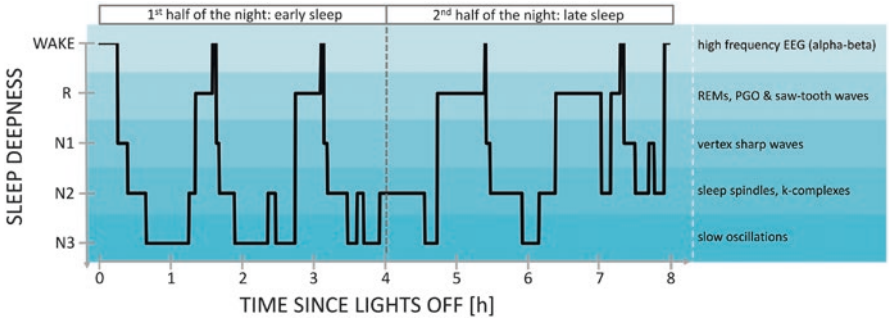

Fig. 9.1 A hypnogram illustrating a healthy human sleep cycle. The figure depicts the different sleep stages over 8 h of nocturnal sleep. As sleep is under circadian control by the inner clock (suprachiasmatic nucleus, SCN), the early sleep period is dominated by slow-wave (N3) sleep, whereas the later sleep is characterized by high amounts of REM (R) sleep. To the right, typical EEG graphoelements are highlighted for each sleep stage. In addition to certain EEG patterns, some of the sleep stages also have characteristic EMG and eye activity patterns, i.e., WAKE, high muscle tone, blinks; N1, eye rolling; and REM, muscle atonia with rare muscle twitches. *R* rapid eye movement sleep, *EEG* electroencephalography, *EMG* electromyography, *REMs* rapid eye movements, *PGO* ponto-geniculo-occipital waves

The advantage of EEG over hemodynamic brain responses (like functional magnetic resonance imaging, fMRI) includes its high temporal resolution and its noninvasive nature, along with its easy portability and low cost. Its main limitation is the spatial resolution and current lack of specificity (diffuse slowing of background rhythms is, for example, seen in various encephalopathies regardless of the etiology). High-density EEG allows better spatial source reconstruction, yet the spatial resolution of fMRI including the assessment of deep brain structures remains unreachable.

It is discussed that one can directly infer about preserved functions or brain areas given the existence of certain sleep-specific PSG graphoelements (i.e., brain activation micro-patterns; see also Fig. 9.1). For example, it has been suggested that the amount or intensity of sleep spindles reflects intact and efficiently connected thalamocortical networks [7, 8], which is also supported by recent data associating high general cognitive and memory abilities to high spindle activity during the night [9, 10]. Furthermore, the presence of REM may be indicative for preserved functioning of the pontine tegmentum in the brainstem [7, 8], and the presence of slow oscillations (to not be mixed up with triphasic waves often observed in DOC patients) suggests intact functioning of certain thalamocortical loops and brainstem nuclei [11]. This pattern of reasoning may be especially interesting in the field of DOC. Some others even suggested for DOC patients that the shape of slow oscillations or the frequency of sleep spindles might reflect the preservation of the thalamocortical system and state of consciousness (see Fig. 9.2) [12].

With respect to the function of sleep, it has been proposed that besides “offline” neuronal plasticity for memory consolidation, one of the major functions of sleep is

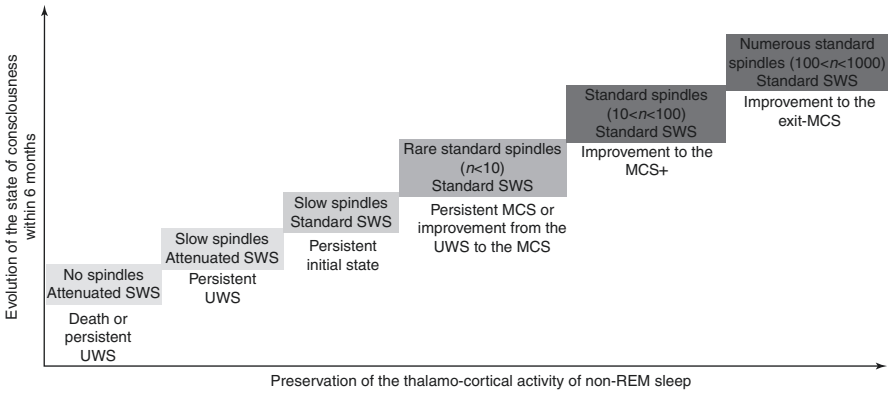

Fig. 9.2 Model predicting DOC outcome according to prevalence of NREM sleep elements. It is postulated that the amplitude of slow oscillations as well as the frequency of sleep spindles reflect preservation of the thalamocortical system and even the state of consciousness. *UWS* unresponsive wakefulness syndrome, *MCS* minimally conscious state, *SWS* slow-wave sleep. Reprinted with permission from [12]

to restore general homeostasis and to stabilize neuronal connections. Therefore, the presence of sleep in DOC patients suggests revival of circadian rhythmicity and might be associated to a higher probability of recovery.

Circadian Rhythms in DOC Patients

On a daily basis, preservation of circadian sleep-wake cycles in DOC patients is typically indirectly inferred by simple behavioral observations of prolonged periods of eye opening or closing. However, to conduct more precise investigations of circadian rhythms in this population, more direct measures would need to be acquired, including SCN activity and its controlled pineal hormone melatonin. To date only a handful of studies conducted in intensive care units (ICU) indicate the loss of circadian secretion of melatonin in sedated unresponsive patients [13, 14]. The detection of changes in hormonal plasma levels (e.g., melatonin, cortisol) and temperature, along with the assessment of blood pressure, heart rate, and motor behavior, should be performed in the future to accurately outline circadian variations in DOC. However, despite the importance of the presence of sleep-wake cycles for differential diagnosis, there is little empirical evidence that DOC patients actually exhibit classical sleep phenomena or display circadian rhythms resembling healthy individuals.

Past studies reported day to night motor activity differences in a majority of UWS as well as MCS patients—with significantly clearer signs for circadian rhythms in the latter group—but not in coma patients [15, 16]. In EEG studies day-night brain state differences were reported in some, but not all UWS and MCS

patients [12, 17, 18]. Furthermore, it was shown that heart rate and blood pressure do not show the typical nocturnal decrease during nightly hours in traumatic UWS patients [19]. Another study in persistent UWS patients showed significant circadian changes in body temperature and urinary excretion of hormones and sodium, but did not observe changes in blood pressure or pulse rate [20]. A more recent study by Bekinschtein and colleagues [21] reported that while UWS patients with traumatic brain injury exhibited well-formed circadian temperature rhythms, patients with anoxic-hypoxic origin demonstrated no cycles or rhythmic behavior. These findings suggest that preservation of circadian rhythms may not only vary with the patients' state of consciousness but also the extent of their individual brain damage.

Altered Sleep in DOC

The question thus arises whether and in which ways sleep in severely brain-injured patients is being altered. Although it is well known that sleep abnormalities are common in critically ill patients, their mechanisms remain poorly understood, and their fine-grained characterizations are still missing [22].

From a behavioral point of view, normal sleep is usually preceded by the search of a safe place, a progressive but reversible decrease of responsiveness to external stimuli, and a decrease of motor output. In DOC, assessing these behavioral criteria is challenging and rarely conclusive.

From an electrophysiological point of view, little is known about UWS, MCS, or LIS sleep. Moreover, since the traditional sleep scoring rules are hardly applicable in case of DOC patients, the classification of sleep and the existence of sleep-specific PSG graphoelements remain a matter of scientific debate. It appears that the existence of sleep and its characterization in DOC is a most challenging issue as these patients do not show the normal behavioral, physiological, and regulatory signs of sleep. Some authors have used traditional sleep criteria to analyze PSG data in DOC [18, 23–25]. However, the various forms of brain damage which may result in a relatively similar clinical appearance of the unconscious state may differ widely with respect to altered brain activity and consequently observable sleep patterns. We therefore believe that it is highly needed to revise and update these scoring criteria if they are intended for differential diagnosis or even prognosis in DOC states.

It is also known that in brain-injured patients, about half of total sleep time occurs during the daytime with circadian rhythm often being significantly diminished or even lost. Compared to healthy volunteers, these patients generally exhibit more frequent arousals and awakenings, as well as less rapid eye movement (REM) and classical deep N3 NREM sleep [26]. Yet, even this statement is difficult to make as unusual eye movements and dominant delta or theta oscillations in the

DOC background make reliable sleep staging impossible. Compared to healthy individuals, DOC patients do not appear to exhibit normal arousals or cyclic alternating patterns (CAPs), and if changes are observed, they may be considerably slowed, lasting a number of seconds or even minutes. Arousal alternations are often more extreme than normally and may even become life-threatening, especially if occurring in the vegetative system (e.g., involving cerebrospinal fluid pressure increase) [27].

UWS

Patients in UWS often show severe sleep fragmentation, which is likely caused by structural changes in brain areas responsible for sleep maintenance, as well as strongly diminished or absent sleep spindling [28, 29]. However, patients close to remission often show reappearance of NREM and REM signs, together with an increase in total sleep time, as well as sleep spindle activity [30]. With regard to REM, these patients exhibit significantly less phasic REM events such as actual rapid eye movements and chin or leg muscle twitches [24].

Yet, the range of PSG graphoelements reported in the literature varies widely. To just give an example, the reported detections of NREM sleep spindles vary between 0 out of 5 [31], 1 out of 8 [32], 3 out of 11 [33], 4 out of 8 [34], 7 out of 10 (mainly with frequencies below 10 Hz; [12]), 15 out of 27 [18], and even 24 out of 32 [35] in UWS patients. Slow oscillations (sometimes mixed with delta waves up to 4 Hz in the respective studies) are reported in none out of 5 [31], in 4 out of 11 [33], or in 9 out of 10 (although mainly with amplitudes below 75 μV) [12] UWS patients. In a more recent study, the presence of slow-wave sleep (SWS) was defined as the occurrence of delta waves (>50 μV, <4 Hz) over 20% of any 30s epoch, which resulted in two out of eight UWS subjects showing SWS sleep [34]. Furthermore, REM sleep is observed in none out of 5 [31], 2 out of 8 [32], 3 out of 10 [12], 2 out of 8 [34], or 4 out of 27 [18] UWS patients. It has to be mentioned that to our experience it is impossible to reliably stage REM sleep in these severely brain-injured patients as rapid eye movements are often asynchronous between both eyes and rarely show REM patterns comparable to healthy individuals. The absence of EMG muscle tone is even harder to use as REM criterion given frequent spastic activity, artifacts, and/or the interaction with anti-spasticity medication in these patients. Recent investigation of K-complexes revealed their present in 1 out of 8 [32] and in 15 of 27 [18] UWS patients. Altogether these data reflect the high heterogeneity which most likely is related to the subjectivity inherent to sleep staging as well as the attempt to individually adjust sleep staging criteria (e.g., spindles <10 Hz or slow waves <75 μV) in order to allow sleep pattern classification in DOC patients in the first place.

MCS

As stated previously, the term "MCS" was only established in 2002; therefore, most of the present literature addressing sleep in DOC patients is missing the MCS entity. In the few studies available, sleep spindles were detected in 15 out of 20 [33], 18 out of 23 [34], all 6 [31, 32], all 10 (sometimes below 10 Hz) [12], or all out of 5 [18] MCS patients. Likewise, slow oscillations are reported being present in 15 out of 20 [33], all out of 6 [31], or all out of 10 (sometimes below 75 μV) [12] MCS patients, whereas SWS in general was observed in 13 out of 23 MCS subjects [34]. Furthermore, REM sleep was observed in 9 out of 23 [34], 5 out of 6 [31, 32], 9 out of 10 [12], and all out of 5 [18] MCS patients. K-complexes were detected in all five [18] and in all six [32] studied MCS patients. Interestingly, these sleep-specific EEG patterns were present in most, but not all patients who have emerged from MCS (EMCS). More specifically, sleep spindles were identified in 12, REM sleep in 6, and SWS in 9 [34] out of 13 MCS subjects.

LIS

The literature about sleep in LIS patients is especially rare. The observed spectrum of altered sleep in LIS can vary from almost normal sleep patterns [36] to hyposomnia [37], disorganized NREM sleep [38–42], or complete REM absence [38, 39, 42, 43]. This wide spectrum is most likely explained by differences in the exact location and extent of causative lesions. In a recent study, preserved sleep spindles and delta waves were identified in one investigated LIS patient [33].

Thus, LIS patients can present in rare cases no major sleep abnormalities although severe neurological deficits are evident. Specifically, it appears that the more extended the pontine lesion, the more pronounced the sleep disturbance, especially concerning REM. Lesion severity increases in case of bilateral or dorsal extensions, and of pontine tegmentum involvement, especially if the serotonin-releasing raphe nuclei of the brainstem (medial portion of the reticular formation) are affected.

Challenges for Sleep Research in DOC

In addition to brain injury, considerable sleep disruption including frequent arousals, awakenings, or enhanced sleep fragmentation also arises from hospital environments itself [22, 44]. Mechanical ventilation, exposure to light, noise, and nursing activities are all factors that can influence sleep in the ICU [7]. An inherent problem to sleep studies in DOC is also that daytime sleep is often uncontrolled or light levels are similar over the day-night period which may result in decreased amounts of sleep during the nightly recording and evaluation times. Altogether these factors

will likely result in a worsening of sleep quality and even serious sleep deprivation in a situation where optimal sleep would be necessary for brain recovery and brain plasticity changes, functions specifically ascribed to nightly sleep in the current literature (for review see: [45]).

In this context important to note is also the fact that sleep deprivation itself is known to have negative impact on immune and endocrine functions. It also induces sympathetic activation and elevation of blood pressure, which in turn can increase morbidity. Moreover sleep deprivation is known to have major and devastating impacts on mood, daytime fatigue, and residual cognitive functioning. This is specifically important when considering this in the context of MCS or LIS patients who are partly or even completely aware of their environment.

Moreover, recording good quality PSG signals in DOC is very challenging due to artifacts caused by strong sweating, thermal dysregulation, skin and skull lesions, or electrical artifacts caused by medical equipment. It is also to note that EEG is often heavily contaminated by uncontrolled eye movements and muscle activation occurring in DOC. Sophisticated correction methods, for example, various independent component analysis algorithms, may be necessary in order to obtain clean EEG data for in-depth analysis and scientific data interpretation.

Treatment and Rehabilitation

Sleep has been repeatedly shown to be beneficial for cognition [46] and especially memory consolidation [45, 47]. Experimentally induced low-frequency brain activity resembling deep sleep has been found to improve recovery of cognitive functions after brain injury, possibly through mitigation of diffuse axonal injury [48].

Even after recovering consciousness (exit-MCS or recovered state), patients still suffer from various sleep disturbances. Insomnia-like sleep complaints (i.e., sleeplessness) are reported as much as hypersomnia-like complaints (i.e., excessive amount of sleepiness) and are probably physiologically linked to the structural changes of brain arousal systems [49–53]. Yet, as seen in normal insomnia patients, recovered DOC patients often overestimate the degree of their sleep disturbance as revealed by comparison of subjective (sleep diaries) and objective (actigraphy, PSG) sleep data [26]. Besides these alterations, sleep pattern and sleep onset latency modifications are common, with only deep NREM sleep being widely preserved [54–57].

Treatment attempts for sleep disturbance in DOC appear to be rather scarce. Although for short-term treatment of sleep disorders the prescription of hypnotic medications may be an effective approach, long-term use of these medications is not suggested due to the unknown long-term effects on neuronal tissue. Non-pharmacological treatments like instrumental conditioning of specific brain oscillations (neurofeedback) [58, 59] may offer an alternative, yet are challenging as they also require the capacity to learn with at least very long treatment periods (>20 sessions).

More practically and from a clinical endpoint, it can be proposed to increase awareness of clinical staff on the importance of sleep hygiene, which should further promote improvement in attitudes and ultimately result in better adjustment of patients' environments for proper sleep [60].

Diagnostic and Prognostic Value of Sleep

Early studies on DOC suggested that the presence of certain EEG patterns may be a reliable marker for favorable outcome [23, 61] with the magnitude of observed sleep alterations being related to injury severity. It was reported that sleep patterns continue to normalize and become more "complex" (i.e., NREM-REM alterations, reappearance of sleep spindles, etc.) during rehabilitation, sometimes even in direct relation to patients' cognitive recovery [62]. Besides these early studies [23, 61], also later findings support the view that the complexity of identified sleep patterns [25, 35, 63–66] carries prognostic information for later outcome. Especially REM elements (rapid ocular movements, muscle twitches, sawtooth waves) alternating regularly with NREM elements as well as certain NREM elements such as K-complexes and sleep spindles have been related to good outcome (full recovery or only mild disability) [25, 35, 64]. Kang and colleagues even found the presence of sleep spindles in UWS patients to have the highest sensitivity (among five significant variables) for predicting recovery of awareness in a 1-year period [35]. This quite good prognosis might be explained by the preservation of thalamocortical functioning which underlies spindle generation [67]. In contrast, patients showing only monophasic EEG (i.e., continuous low-voltage theta-delta activity) or CAPs indicating arousal instability during NREM, in the absence of classical PSG graphoelements, have been associated with bad outcome (death or severe disabilities) [25]. At the same time it is interesting to note that in a recent study Arnaldi and colleagues found that among others the complexity of sleep structure is a significant predictor for follow-up assessment, whereas gender, etiology, or site of the lesion is not [64].

Future studies should therefore aim for long-term PSG recordings together with circadian measures in well-documented DOC patients. Ultimately these tools might help to further differentiate the various DOC states and especially complement the often difficult distinction between UWS and MCS patients (for review also see [7]).

Summary

In summary, DOC patients are often linked to alterations in sleep architecture and their associated graphoelements. In the coma state, the patient by definition shows no eye-opening and no sleep-wake cycling. However, certain NREM and REM graphoelements may emerge, yet in an often unusual generalized form. In UWS patients show transient periods of eye-opening and sleep-wake cycles. However,

few studies provide empirical evidence of the residual sleep architecture. Most literature exists for the recovery from coma and deals with the reappearance of NREM graphoelements such as sleep spindles.

The study of sleep is also of particular interest in DOC as it might allow identifying underlying neuronal lesions linked to specific PSG graphoelements. Therefore, changes in CAPs may indicate that arousal control mechanisms have been injured or severely altered. The pathophysiological mechanism of spindle coma has been related to the pontine raphe nuclei and thalamocortical circuits together with the impairment of the ascending reticular activating system located in the midbrain which usually maintains arousal [68–70]. The absence of spindles in coma presumably results from the interruption of either the ascending reticulo-thalamocortical pathway or thalamocortical loops. Present REM on the other hand may reflect residual functioning of brainstem nuclei including pons and adjacent portions of the midbrain. Last but not least, the absence of sleep-wake cycles, which is also typical in comatose patients, is associated with brainstem dysfunction and might be informative of lack of hypothalamic and SCN functioning. However, it has to be noted that to date the empirical evidence for such claims is scarce or even absent.

Likewise, there are no accepted PSG patterns which reliably define each of the reviewed DOC states. In addition, there is very little evidence indicating whether sleep in DOC is still under normal circadian and homeostatic control. From a methodological point of view, it is to be noted that studying sleep in DOC is a challenging endeavor. Long-term PSG of DOC patients in clinical or rehabilitation centers is difficult because of various artifacts arising from environmental factors and nursing activities or from clinical instability or mandatory pharmacological treatment.

Altogether, the characterization of sleep and its relationships with arousal, homeostasis, and circadian rhythmicity is, in our view, essential in order to better understand the various DOC states and might by themselves offer complementary diagnostic and prognostic information or even guide the direction of future treatment attempts.

References

1. Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, et al. The minimally conscious state: definition and diagnostic criteria. Neurology. 2002;58(3):349–53.
2. Brenner RP. The interpretation of the EEG in stupor and coma. Neurologist. 2005;11(5):271–84.
3. Hansotia P, Gottschalk P, Green P, Zais D. Spindle coma: incidence, clinicopathologic correlates, and prognostic value. Neurology. 1981;31(1):83–7.
4. Monti MM, Laureys S, Owen AM. The vegetative state. BMJ. 2010;341:c3765.
5. Bruno M-A, Gosseries O, Ledoux D, Hustinx R, Laureys S. Assessment of consciousness with electrophysiological and neurological imaging techniques. Curr Opin Crit Care. 2011;17(2):146–51.
6. Berry R, Brooks R, Gamaldo C. The AASM Manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Version 2.0. Darien: American Academy of Sleep Medicine; 2012.

7. Cologan V, Schabus M, Ledoux D, Moonen G, Maquet P, Laureys S. Sleep in disorders of consciousness. Sleep Med Rev. 2010;14(2):97–105.
8. Bekinschtein T, Cologan V, Dahmen B, Golombek D. You are only coming through in waves: wakefulness variability and assessment in patients with impaired consciousness. Prog Brain Res. 2009;177:171–89.
9. Schabus M, Hödlmoser K, Gruber G, Sauter C, Anderer P, Klösch G, et al. Sleep spindle-related activity in the human EEG and its relation to general cognitive and learning abilities. Eur J Neurosci. 2006;23(7):1738–46.
10. Bodizs R, Kis T, Lazar AS, Havran L, Rigo P, Clemens Z, et al. Prediction of general mental ability based on neural oscillation measures of sleep. J Sleep Res. 2005;14(3):285–92.
11. Dang-Vu TT, Schabus M, Desseilles M, Albouy G, Boly M, Darsaud A, et al. Spontaneous neural activity during human slow wave sleep. Proc Natl Acad Sci U S A. 2008;105(39): 15160–5.
12. Cologan V, Drouot X, Parapatics S, Delorme A, Gruber G, Moonen G, et al. Sleep in the unresponsive wakefulness syndrome and minimally conscious state. J Neurotrauma. 2013;30(5): 339–46.
13. Mundigler G, Delle-Karth G, Koreny M, Zehetgruber M, Steindl-Munda P, Marktl W, et al. Impaired circadian rhythm of melatonin secretion in sedated critically ill patients with severe sepsis. Crit Care Med. 2002;30(3):536–40.
14. Guaraldi P, Sancisi E, La Morgia C, Calandra-Buonaura G, Carelli V, Cameli O, et al. Nocturnal melatonin regulation in post-traumatic vegetative state: a possible role for melatonin supplementation? Chronobiol Int. 2014;31(5):741–5.
15. De Weer AS, Da Ros M, Berre J, Melot C, Goldman S, Peigneux P. Environmental influences on activity patterns in altered states of consciousness. Eur J Neurol. 2011;18(12):432–4.
16. Cruse D, Thibaut A, Demertzi A, Nantes JC, Bruno M-A, Gosseries O, et al. Actigraphy assessments of circadian sleep-wake cycles in the Vegetative and Minimally Conscious States. BMC Med. 2013;11(1):18.
17. Isono M, Wakabayashi Y, Fujiki MM, Kamida T, Kobayashi H. Sleep cycle in patients in a state of permanent unconsciousness. Brain Inj. 2002;16(8):705–12.
18. de Biase S, Gigli GL, Lorenzut S, Bianconi C, Sfreddo P, Rossato G, et al. The importance of polysomnography in the evaluation of prolonged disorders of consciousness: sleep recordings more adequately correlate than stimulus-related evoked potentials with patients' clinical status. Sleep Med. 2014;15(4):393–400.
19. Pattoneri P, Tirabassi G, Pela G, Astorri E, Mazzucchi A, Borghetti A. Circadian blood pressure and heart rate changes in patients in a persistent vegetative state after traumatic brain injury. J Clin Hypertens (Greenwich). 2005;7(12):734–9.
20. Fukudome Y, Abe I, Saku Y, Matsumura K, Sadoshima S, Utunomiya H, et al. Circadian blood pressure in patients in a persistent vegetative state. Am J Phys. 1996;270(5 Pt 2):R1109–14.
21. Bekinschtein TA, Golombek DA, Simonetta SH, Coleman MR, Manes FF. Circadian rhythms in the vegetative state. Brain Inj. 2009;23(11):915–9.
22. Parthasarathy S, Tobin MJ. Sleep in the intensive care unit. Intensive Care Med. 2004;30(2):197–206.
23. Chatrian GE, White Jr LE, Daly D. Electroencephalographic patterns resembling those of sleep in certain comatose states after injuries to the head. Electroencephalogr Clin Neurophysiol. 1963;15:272–80.
24. Oksenberg A, Gordon C, Arons E, Sazbon L. Phasic activities of rapid eye movement sleep in vegetative state patients. Sleep. 2001;24(6):703–6.
25. Valente M, Placidi F, Oliveira AJ, Bigagli A, Morghen I, Proietti R, et al. Sleep organization pattern as a prognostic marker at the subacute stage of post-traumatic coma. Clin Neurophysiol. 2002;113(11):1798–805.
26. Ouellet MC, Savard J, Morin CM. Insomnia following traumatic brain injury: a review. Neurorehabil Neural Repair. 2004;18(4):187–98.

27. Evans BM. What does brain damage tell us about the mechanisms of sleep? J R Soc Med. 2002;95(12):591–7.
28. Giubilei F, Formisano R, Fiorini M, Vitale A, Faroni J, Toni D, et al. Sleep abnormalities in traumatic apallic syndrome. J Neurol Neurosurg Psychiatry. 1995;58(4):484–6.
29. D'Aleo G, Bramanti P, Silvestri R, Saltuari L, Gerstenbrand F, Di Perri R. Sleep spindles in the initial stages of the vegetative state. Ital J Neurol Sci. 1994;15(7):347–51.
30. D'Aleo G, Saltuari L, Gerstenbrand F, Bramanti P. Sleep in the last remission stages of vegetative state of traumatic nature. Funct Neurol. 1994;9(4):189–92.
31. Landsness E, Bruno MA, Noirhomme Q, Riedner B, Gosseries O, Schnakers C, et al. Electrophysiological correlates of behavioural changes in vigilance in vegetative state and minimally conscious state. Brain. 2011;134(Pt 8):2222–32.
32. Aricò I, Naro A, Pisani LR, Leo A, Muscarà N, De Salvo S, et al. Could combined sleep and pain evaluation be useful in the diagnosis of disorders of consciousness (DOC)? Preliminary findings. Brain Inj. 2016;30(2):159–63.
33. Malinowska U, Chatelle C, Bruno M-A, Noirhomme Q, Laureys S, Durka PJ. Electroencephalographic profiles for differentiation of disorders of consciousness. Biomed Eng Online. 2013;12(1):109.
34. Forgacs PB, Conte MM, Fridman EA, Voss HU, Victor JD, Schiff ND. Preservation of electroencephalographic organization in patients with impaired consciousness and imaging-based evidence of command-following. Ann Neurol. 2014;76(6):869–79.
35. Kang X, Li L, Wei D, Xu X, Zhao R, Jing Y, et al. Development of a simple score to predict outcome for unresponsive wakefulness syndrome. Crit Care. 2014;18:R37.
36. Oksenberg A, Soroker N, Solzi P, Reider-Groswasser I. Polysomnography in locked-in syndrome. Electroencephalogr Clin Neurophysiol. 1991;78(4):314–7.
37. Guilleminault C, Cathala JP, Castaigne P. Effects of 5-hydroxytryptophan on sleep of a patient with a brain-stem lesion. Electroencephalogr Clin Neurophysiol. 1973;34(2):177–84.
38. Markand ON, Dyken ML. Sleep abnormalities in patients with brain stem lesions. Neurology. 1976;26(8):769–76.
39. Cummings JL, Greenberg R. Sleep patterns in the "locked-in" syndrome. Electroencephalogr Clin Neurophysiol. 1977;43(2):270–1.
40. Freemon FR, Salinas-Garcia RF, Ward JW. Sleep patterns in a patient with a brain stem infarction involving the raphe nucleus. Electroencephalogr Clin Neurophysiol. 1974;36(6):657–60.
41. Autret A, Laffont F, de Toffol B, Cathala HP. A syndrome of REM and non-REM sleep reduction and lateral gaze paresis after medial tegmental pontine stroke. Computed tomographic scans and anatomical correlations in four patients. Arch Neurol. 1988;45(11):1236–42.
42. Tamura K, Karacan I, Williams RL, Meyer JS. Disturbances of the sleep-waking cycle in patients with vascular brain stem lesions. Clin Electroencephalogr. 1983;14(1):35–46.
43. Lavie P, Pratt H, Scharf B, Peled R, Brown J. Localized pontine lesion: nearly total absence of REM sleep. Neurology. 1984;34(1):118–20.
44. Cabello B, Thille A-W, Mancebo J. Sommeil en réanimation. Réanimation. 2007;16(1):61–6.
45. Diekelmann S, Born J. The memory function of sleep. Nat Rev Neurosci. 2010;11(2):114–26.
46. Hobson JA. Sleep is of the brain, by the brain and for the brain. Nature. 2005;437(7063):1254–6.
47. Sejnowski TJ, Destexhe A. Why do we sleep? Brain Res. 2000;886(1–2):208–23.
48. Morawska MM, Büchele F, Moreira CG, Imbach LL, Noain D, Baumann CR. Sleep modulation alleviates axonal damage and cognitive decline after rodent traumatic brain injury. J Neurosci. 2016;36(12):3422–9.
49. George B, Landau-Ferey J. Twelve months' follow-up by night sleep EEG after recovery from severe head trauma. Neurochirurgia (Stuttg). 1986;29(2):45–7.
50. Keshavan MS, Channabasavanna SM, Reddy GN. Post-traumatic psychiatric disturbances: patterns and predictors of outcome. Br J Psychiatry. 1981;138:157–60.

51. Cohen M, Oksenberg A, Snir D, Stern MJ, Groswasser Z. Temporally related changes of sleep complaints in traumatic brain injured patients. J Neurol Neurosurg Psychiatry. 1992;55(4): 313–5.
52. Clinchot DM, Bogner J, Mysiw WJ, Fugate L, Corrigan J. Defining sleep disturbance after brain injury. Am J Phys Med Rehabil. 1998;77(4):291–5.
53. Fichtenberg NL, Zafonte RD, Putnam S, Mann NR, Millard AE. Insomnia in a post-acute brain injury sample. Brain Inj. 2002;16(3):197–206.
54. Guilleminault C, Yuen KM, Gulevich MG, Karadeniz D, Leger D, Philip P. Hypersomnia after head-neck trauma: a medicolegal dilemma. Neurology. 2000;54(3):653–9.
55. Masel BE, Scheibel RS, Kimbark T, Kuna ST. Excessive daytime sleepiness in adults with brain injuries. Arch Phys Med Rehabil. 2001;82(11):1526–32.
56. Ouellet MC, Morin CM. Subjective and objective measures of insomnia in the context of traumatic brain injury: a preliminary study. Sleep Med. 2006;7(6):486–97.
57. Ouellet MC, Beaulieu-Bonneau S, Morin CM. Insomnia in patients with traumatic brain injury: frequency, characteristics, and risk factors. J Head Trauma Rehabil. 2006;21(3): 199–212.
58. Hoedlmoser K, Dang-Vu TT, Desseilles M, Schabus M. Non-pharmacological alternatives for the treatment of insomnia—instrumental EEG conditioning, a new alternative? In: Soriento YE, editor. Melatonin, sleep and insomnia. New York: Nova Science; 2011.
59. Schabus M, Heib DP, Lechinger J, Griessenberger H, Klimesch W, Pawlizki A, et al. Enhancing sleep quality and memory in insomnia using instrumental sensorimotor rhythm conditioning. Biol Psychol. 2014;95:126–34.
60. Massengale JP. The role of nursing practice in promoting sleep during brain injury rehabilitation hospitalization. Minneapolis: Walden University; 2015.
61. Bergamasco B, Bergamini L, Doriguzzi T, Sacerdote I. The sleep cycle in coma: prognostic value. Electroencephalogr Clin Neurophysiol. 1968;25(1):87.
62. Ron S, Algom D, Hary D, Cohen M. Time-related changes in the distribution of sleep stages in brain injured patients. Electroencephalogr Clin Neurophysiol. 1980;48(4):432–41.
63. Evans BM, Bartlett JR. Prediction of outcome in severe head injury based on recognition of sleep related activity in the polygraphic electroencephalogram. J Neurol Neurosurg Psychiatry. 1995;59(1):17–25.
64. Arnaldi D, Terzaghi M, Cremascoli R, De Carli F, Maggioni G, Pistarini C, et al. The prognostic value of sleep patterns in disorders of consciousness in the sub-acute phase. Clin Neurophysiol. 2016;127(2):1445–51.
65. Sebastiano DR, Panzica F, Visani E, Rotondi F, Scaioli V, Leonardi M, et al. Significance of multiple neurophysiological measures in patients with chronic disorders of consciousness. Clin Neurophysiol. 2015;126(3):558–64.
66. Avantaggiato P, Molteni E, Formica F, Gigli GL, Valente M, Lorenzut S, et al. Polysomnographic sleep patterns in children and adolescents in unresponsive wakefulness syndrome. J Head Trauma Rehabil. 2015;30(5):334–46.
67. Schabus M, Dang-Vu TT, Albouy G, Balteau E, Boly M, Carrier J, et al. Hemodynamic cerebral correlates of sleep spindles during human non-rapid eye movement sleep. Proc Natl Acad Sci U S A. 2007;104(32):13164–9.
68. Britt Jr CW, Raso E, Gerson LP. Spindle coma, secondary to primary traumatic midbrain hemorrhage. Electroencephalogr Clin Neurophysiol. 1980;49(3–4):406–8.
69. Britt Jr CW. Nontraumatic "spindle coma": clinical, EEG, and prognostic features. Neurology. 1981;31(4):393–7.
70. Seet RC, Lim EC, Wilder-Smith EP. Spindle coma from acute midbrain infarction. Neurology. 2005;64(12):2159–60.

Chapter 10
Sensory Stimulation Program

Haibo Di and Caroline Schnakers

Abstract Taking care of patients recovering from coma is challenging, with current therapeutic treatments being neither well developed nor well validated. Sensory stimulation is a long-established treatment developed for severely brain-injured patients. Numerous studies have investigated the use of sensory stimulation programs in patients with disorders of consciousness. However, the efficacy of such treatment is still currently debated. We will introduce the theoretical principles underlying these therapeutic treatment programs as well as the studies assessing their clinical interest. We will also discuss the limitations of those treatments and consider future directions for clinical research.

Introduction

Progress in intensive care has led to an increase in the number of patients who survive severe brain injury. Although the majority of patients recover in the first days following coma, some of these patients stay in a disorder of consciousness. Until now, no treatment has shown its efficacy in patients with severe brain injury, with the exception of one pharmacological agent (i.e., amantadine) [1]. Recovery of consciousness is therefore one of the biggest challenges facing clinicians [2]. For years, sensory stimulation programs have been the most frequently applied treatment

H. Di, Ph.D.
Physiology Department, International Vegetative State and Consciousness Science Institute, Hangzhou Normal University, Xuelin, 310036 Hangzhou, Zhejiang, China
e-mail: dihaibo@yahoo.com.cn

C. Schnakers, Ph.D. (✉)
Department of Neurosurgery, University of California Los Angeles, Los Angeles, CA, USA

Department of Research, Casa Colina Hospital and Centers for Healthcare, Pomona, CA, USA
e-mail: cschnakers@ucla.edu; cschnakers@casacolina.org

C. Schnakers, S. Laureys (eds.), *Coma and Disorders of Consciousness*,
DOI 10.1007/978-3-319-55964-3_10

during patients' neurorehabilitation [3]. These programs are based on the idea that an enriched environment benefits brain plasticity and improves the recovery of injured brains. Theories of brain plasticity, which suggest that an adult injured brain has the capacity to reorganize itself to compensate for the affected regions, have broadly been accepted for several years [4]. The most famous case illustrating this phenomenon is the case of Terry Wallis [5]. This patient remained in a minimally conscious state for 19 years after a traumatic brain injury and yet recovered both functional verbal communication and functional motor activity. A study of this case revealed a neural change, mainly involving the precuneus which is known to be related to consciousness, suggesting that this spectacular recovery could be explained by brain plasticity [5]. These results stress the importance of developing therapeutic interventions that intensify brain plasticity in severely brain-injured adults to reach full recovery of consciousness.

Providing sensory stimulation (e.g., auditory, verbal, visual, olfactory, tactile, and gustatory) to the patient may potentially stimulate affected neural networks, accelerate brain plasticity, and avoid a sensory deprivation that could slow down the patient's consciousness recovery. The efficacy of such treatment is, however, still currently debated. We will introduce the theoretical principles underlying sensory stimulation treatments as well as the studies assessing their clinical interest. We will also discuss the limitations of those treatments and consider future directions for clinical research.

Theoretical Principles

Sensory stimulation through interaction with the environment from birth to old age has a key role in refining the neuronal circuitry required for normal brain function. Rosenzweig and colleagues introduced "environmental enrichment" in the field of animal research four decades ago to investigate the influence of environment on brain and behavior and showed that the morphology and physiology of the brain can be altered by modifying the quality and intensity of environmental stimulation [6, 7]. An enriched environment is an environment with enhanced novel and complex stimulation (e.g., toys, tunnels, nesting material, and stairs which may vary in shape, size, smell, and color) relative to a standard environment, providing the animals with optimal conditions for enhanced exploration, cognitive activity, and physical exercise [7]. Many studies have shown that enriched environment elicits brain changes such as increase in cortical thickness and weight [8, 9], size of the cell soma and nucleus, dendritic arborization, length of dendritic spines [10–12], and synaptic size and number [13–15]. In animal models, exposure to such environment has shown to be beneficial for nervous system disorders, including different types of brain injury [16–18]. Indeed, evidence suggests that the recovery of cognitive (e.g., learning and memory) and motor functions following experimental brain lesion is

enhanced by this technique [19–21]. Enriched environment following brain injury also has beneficial effects on the brain, such as decreasing lesion size or enhancing dendritic branching [22–24].

The results we described above hence encourage the use of enriched environment in order to avoid sensory deprivation and promote brain plasticity. Sensory stimulation would allow changes in the structure and the functioning of the nervous system and also in the behaviors that an individual can demonstrate to interact with his/her surroundings.

Sensory Stimulation Programs

Considering these principles, the Institutes for the Achievement of Human Potential (IAHP) have introduced sensory stimulation programs in the field of neurorehabilitation. Despite the lack of scientific evidence in human subjects, sensory stimulation programs are based on the principle that they could enhance the rehabilitative process by avoiding environmental deprivation and promoting synaptic reinnervation, thus accelerating the recovery from disorders of consciousness in severely brain-injured patients [25].

Stimulation programs vary from single stimuli of a single sense (unimodal stimulation) to stimulation of all senses using various stimuli (multimodal stimulation) [26]. However, Wood has criticized the therapeutic concepts of the intensive multisensory stimulation programs for patients diagnosed with disorders of consciousness, raising two concerns: the patient's overstimulation and habituation [27, 28]. Stimulation programs could be too demanding on patients with severe brain injury because of the limited capacity for information processing. On the other hand, a variation of stimuli ensures that a stimulus can be distinguished, correctly selected, and processed by the patient. Wood proposes that supporting selective attention is crucial since it mediates information processing [28]. He therefore introduced the more deductive approach of sensory regulation. This approach recommends a careful regulation of stimuli for their intensity and frequency with, for instance, reduction of the background sounds of the hospital ward, limited time for using radio and TV, and rest periods at regular intervals. Such a program would also allow the patient to follow highly structured stimulation optimizing her/his aptitude to react and to respond to their environment.

Numerous studies investigated these various sensory stimulation programs in patients with disorders of consciousness. Mostly there seems to be a positive effect of these programs on consciousness recovery [18, 25, 29–39]. These results are, however, often affected by methodological biases and must be considered with caution. Indeed, Lombardi and colleagues assessed the efficacy of sensory stimulation programs in patients diagnosed as being in a coma or in a vegetative state in performing a systematic review of randomized and nonrandomized controlled trials

published from 1966 to 2002 [26]. This meta-analysis reported only three studies with adequate methodologies, the other ones being, for the most part, noncontrolled designs or descriptive case reports.

Two randomized controlled trials examined the effects of multimodal stimulation programs in severely brain-injured populations [33, 39]. Both trials examined visual, auditory, olfactory, and tactile stimuli, additionally with gustatory, kinesthetic, and vestibular stimuli [33] or with kinesthetic and verbal stimuli [39]. Sensory stimulation treatments were applied once to twice per day, for 45–60 min duration per treatment. Coma recovery was examined as the primary outcome, including coma duration and GCS score (Table 10.1). These two studies showed a higher recovery in the experimental groups than in the control groups, suggesting a positive impact of the sensory stimulation programs on the recovery of severely brain-injured patients. A third trial examined treatment that stimulated the five senses for 20 min per day during the entire stay in the intensive care [38]. No significant changes were found in GCS scores, brainstem reflexes (e.g., oculo-cephalic and oculo-vestibular reflexes) or physiological measurements (e.g., skin conductance, respiratory, and heart rates).

The results from this small number of studies are therefore inconclusive and cannot confirm the efficacy of multimodal stimulation for patients recovering from coma [27]. Indeed, besides an insufficient description of the sensory stimulation program applied, the results are somewhat contradictory, the types and dosage of interventions are different, and the primary outcomes examined also differ, making study comparison difficult. Thus, there is no reliable evidence to support sensory stimulation programs in comatose or vegetative patients. Another contributing factor that was not considered in this review was the role of improvements due to spontaneous recovery. Indeed, these studies were mainly performed in the acute or subacute stage, a period during which spontaneous recovery has the highest probability to appear. Due to small sample sizes, none of these studies could ensure a dissociation between improvements attributed to the sensory stimulation treatment and improvements due to spontaneous recovery.

Since 2002, several studies have been published that examine sensory stimulation in the treatment of patients with disorders of consciousness. They nevertheless, for the most part, present the same methodological issues as described above [40–46]. Interestingly, three studies investigated whether the improvements observed after a sensory stimulation program exceeded spontaneous recovery [43–45]. Time series designs (i.e., ABA, ABCBA, and ABABAB paradigms) were used since the treatment was applied and compared to baselines (see Fig. 10.1). Results showed a significant fluctuation of the behavioral responses according to the presence or the absence of the treatment, more complex responses being observed in the presence of treatment. These studies suggest that sensory stimulation programs might have an impact superior to spontaneous recovery on the improvement of consciousness in patients recovering from coma. However, they only included a small number of patients ($n < 15$). Finally, only one study recently investigated the changes in brain activity related to treatment. Pape and colleagues examined the effects of a unimodal stimulation program using familiar auditory stimulation [46]. They found

Table 10.1 Summary of previous studies investigating sensory stimulation program

Reference	Sample size	Cause of injury	Time since injury	Level of consciousness	Design	Main findings after/during treatment
Kater et al. [39]	30	TBI	2 weeks	Mix (GCS 3–14)	Nonrandomized controlled	Better outcome at 3 months post-injury
Mitchell et al. [33]	24	TBI	4–12 days	Mix (GCS 4–6)	Nonrandomized controlled	Shorter duration of coma and increase in the GCS
Johnson et al. [38]	14	TBI	<24 h	Mix (GCS ≤8)	Randomized controlled	No significant changes in the GCS, brainstem reflexes, or physiological measurements
Oh and Seo [43]	5	TBI/NTBI	<3 months	Mix (GCS 3–7)	Time series	Increase in the GCS
Lotze et al. [45]	8	TBI/NTBI	16–126 months	Mix (VS/MCS)	Time series	Improvements in behavioral responses (e.g., response to command)
Di Stefano et al. [44]	12	TBI/NTBI	>1 month	Mix (VS/MCS)	Time series	Greater range of behavioral responses based on the Wessex Head Injury Matrix
Pape et al. [46]	15	TBI	Average of 70 days	Mix (VS/MCS)	Randomized controlled	Improvements in behavioral responses based on the Coma Near Coma Scale and in brain activity based on fMRI recording. Effect size: $d = 1.88$

TBI traumatic brain injury, *NTBI* non-traumatic brain injury, *GCS* Glasgow Coma Scale, *VS* vegetative state, *MCS* minimally conscious state, *fMRI* functional magnetic resonance imaging, *EEG* electroencephalogram

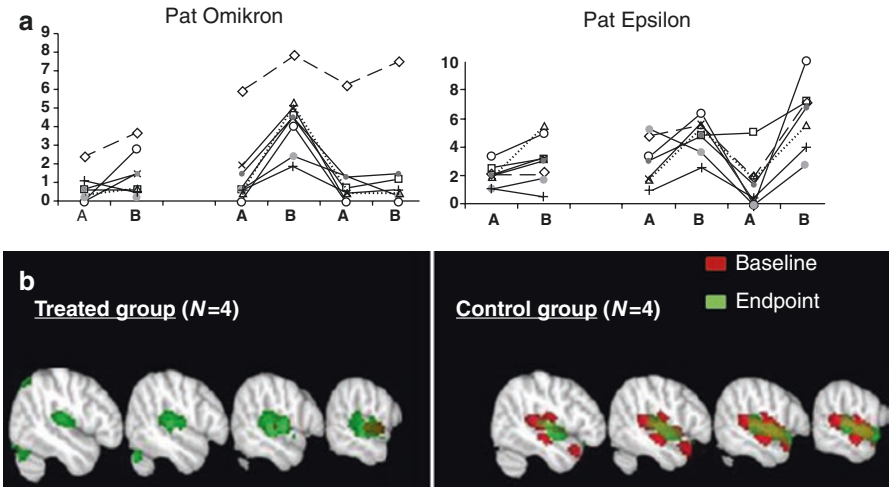

Fig. 10.1 Behavioral and fMRI response to sensory stimulation program. Panel (**a**) illustrates averaged behavioral scores from blinded independent raters during multimodal sensory program in two patients. The *x*-axis describes time (ABABAB design where A = baseline and B = treatment) and the *y*-axis represents the rating scores (0 = no movement, 10 = voluntary movements) [45]. Panel (**b**) illustrates brain activation in response to unimodal sensory (auditory) stimulation, at the baseline and at the end of the study [46]

better neurobehavioral performance in the treated group as compared with the control group. fMRI recordings performed before and after treatment demonstrated higher activation in the language network in the treated group as compared to the control group, suggesting an impact of the sensory stimulation program on the patients' brain recovery (see Fig. 10.1). Findings such as these indicate that supplementing behavioral measures with neuroimaging may expand our understanding of the impact of sensory stimulation with such complex patient populations.

Limitations and Perspectives

The beneficial effects of enriched environment on brain plasticity and cognitive functioning have been demonstrated by animal research. Its impact on human subjects is nevertheless much more challenging to show. The first difference is the control of the environment. It is more difficult to consider all the variables that have potential impact on the patient's recovery in a hospital setting than on a mouse in a cage. Medication, changes in therapy, medical status, or spontaneous recovery are among the variables that are the most difficult to control. Although these are not impossible to account for, most of the studies examining sensory stimulation have

been performed in an acute setting where all those variables are in constant change. The inclusion of a more chronic population would be a way to manage this bias as these patients are more stabilized. We do not imply that changes in treatment or spontaneous recovery are not existent at a chronic stage but that they occur less frequently, and are easier to document and to include in statistical models.

The other weakness of the studies of sensory stimulation is the sample size. Most of the existing studies are case reports or descriptive case series where bias has not been minimized. They do not include a sample size sufficient enough to allow a generalization of the results. Although longitudinal studies may be better suited to answering relevant questions, these require an important investment in time, making difficult for an isolated center to follow more than 30 cases simultaneously while finishing the study within a reasonable time-frame. The solution to that problem would be the development of an international initiative involving a significant amount of centers. This is not impossible since it has been done before for demonstrating the effect of amantadine (a pharmacological agent targeting dopaminergic neurotransmission) on the recovery of patients with severe brain injury [1]. This recent study has been performed with the participation of 11 clinical sites and resulted in the recruitment of 184 patients which were followed during 6 weeks. The study used a randomized double-blind placebo-controlled design. Such sample size and such design represent a phase II clinical trial and allowed to establish the efficacy of the treatment (for more information, see ClinicalTrials.gov).

The use of a control group is difficult to implement when the sample size is low, and the results can be biased by the way the control group was made. The lack of consideration of some variables impacting patients' outcome could lead the researcher to think he sees an effect of treatment when, in fact, the treated group had a better prognosis to start with. In that kind of context, the use of a within subjects times-series design (e.g., ABAB paradigms) is an interesting alternative. Even though this design has its own flaws (such as, "time effect"), it will certainly help to take in account the impact of spontaneous recovery. Several recent studies used this design quite successfully in a few patients and showed a beneficial impact of sensory stimulation, encouraging further investigations [43–45]. However, the use of a controlled design is more efficient when considering large samples since it requires a shorter follow-up. The use of a randomized (rather than matched) control group allow bias allocation to be minimized, balancing both known and unknown prognostic factors, in the assignment of treatments and is an optimal choice when dealing with such a heterogeneous population. Blinding remains another essential component of any rigorous trial so that assessor bias is avoided. It can seem obvious to mention this but only a few studies on sensory stimulation are, in fact, blinded (or double-blinded) [26]. Since finding a placebo to sensory stimulation is not easy, another way to proceed is to have one researcher administer the treatment while another researcher assesses the patients' recovery, independently. In doing so,

the researcher involved in assessing the patient's recovery is blinded on whether or not the patient is in the treated group. Finally, one aspect that has been found useful in a number of exploratory studies [46, 47] and should be considered in the future is the use of neuroimaging techniques (e.g., functional magnetic resonance imaging (fMRI) or electrophysiology). Indeed, showing that treatment-related changes are observed using objective methods is essential to prove that sensory stimulation programs are efficient in improving brain plasticity in patients with disorders of consciousness.

A Potential Alternative: Music Therapy

Recently, music therapy has been presented as another way to stimulate patients. Music has a well-known therapeutic effect on patients with progressive brain disease (such as Alzheimer or Parkinson) or neurodevelopmental disorder (such as autism) and might be a promising tool when treating patients with severe brain injuries [48–51]. Music therapy interventions use live music that can be modified according to patient responsiveness "in the moment." Musical parameters (e.g., tempo, rhythm) are manipulated according to changes in a patient's attention or arousal. Previous studies with DOC populations suggest that music enhanced arousal and attention when compared to white noise or disliked music or when compared to a control nonmusical auditory stimulus, suggesting a potential impact of music therapy on consciousness recovery [47, 52–54]. Research into music therapy with DOC has however been limited due to the lack of behavioral measures that are sensitive to the complex needs of this population [55, 56]. For this reason, single-subject designs and case reports prevail, reporting on behavioral and neurophysiological outcomes.

Conclusion

Initiating multicentric projects is challenging, but it is crucial to determine whether therapies using sensory stimulation are useful interventions for patients with disorders of consciousness, since treatment options are limited. The results from animal research and the preliminary results on sensory stimulation programs and music therapy obtained in human subjects should encourage further investigations. Such initiatives would join the recent interest in the development of treatments for disorders of consciousness, which has been emerging in recent years and which involves neuromodulation therapeutics such as deep brain stimulation (DBS) [57] or transcranial direct current stimulation (tDCS) [58]. The combination of all these scientific findings will certainly help the clinicians to treat efficiently patients with severe brain injury and will, maybe one day, lead us to consider the disorders of consciousness as a problem of the past.

References

1. Giacino JT, Whyte J, Bagiella E, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. N Engl J Med. 2012;366(9):819–26.
2. Whyte J. Disorders of consciousness: the changing landscape of treatment. Neurology. 2014;82(13):1106–7.
3. Tolle P, Reimer M. Do we need stimulation programs as a part of nursing care for patients in "persistent vegetative state"? A conceptual analysis. Axone. 2003;25(2):20–6.
4. Hummel FC, Cohen LG. Drivers of brain plasticity. Curr Opin Neurol. 2005;18(6):667–74.
5. Voss HU, Uluğ AM, Dyke JP, et al. Possible axonal regrowth in late recovery from the minimally conscious state. J Clin Invest. 2006;116(7):2005–11.
6. Rosenzweig MR. Environmental complexity, cerebral change, and behavior. Am Psychol. 1966;21(4):321–32.
7. Rosenzweig MR, Bennett EL, Hebert M, et al. Social grouping cannot account for cerebral effects of enriched environments. Brain Res. 1978;153(3):563–76.
8. Rosenzweig MR, Bennett EL, Krech D. Cerebral effects of environmental complexity and training among adult rats. J Comp Physiol Psychol. 1964;57:438–9.
9. Beaulieu C, Colonnier M. Effect of the richness of the environment on the cat visual cortex. J Comp Neurol. 1987;266(4):478–94.
10. Holloway RL. Dendritic branching: some preliminary results of training and complexity in rat visual cortex. Brain Res. 1966;2(4):393–6.
11. Greenough WT, Volkmar FR, Juraska JM. Effects of rearing complexity on dendritic branching infrontolateral and temporal cortex of the rat. Exp Neurol. 1973;41(2):371–8.
12. Kozorovitskiy Y, Gross CG, Kopil C, et al. Experience induces structural and biochemical changes in the adult primate brain. Proc Natl Acad Sci U S A. 2005;102(48):17478–82.
13. Diamond MC, Krech D, Rosenzweig MR. The effects of an enriched environment on the histology of the rat cerebral cortex. J Comp Neurol. 1964;123:111–20.
14. Mollgaard K, Diamond MC, Bennett EL, et al. Quantitative synaptic changes with differential experience in rat brain. Int J Neurosci. 1971;2(3):113–27.
15. Turner AM, Greenough WT. Differential rearing effects on rat visual cortex synapses. Synaptic and neuronal density and synapses per neuron. Brain Res. 1985;329(1–2):195–203.
16. Johansson BB. Functional outcome in rats transferred to an enriched environment 15 days after focal brain ischemia. Stroke. 1996;27(2):324–6.
17. Koopmans GC, Brans M, Gómez-Pinilla F, et al. Circulating insulin-like growth factor and functional recovery from spinal cord injury under enriched housing conditions. Eur J Neurosci. 2006;23(4):1035–46.
18. Sale A, Berardi N, Maffei L. Enrich the environment to empower the brain. Trends Neurosci. 2009;32(4):233–9.
19. Farrell R, Evans S, Corbett D. Environmental enrichment enhances recovery of function but exacerbates ischemic cell death. Neuroscience. 2001;107:585–92.
20. Hicks RR, Zhang L, Atkinson A, et al. Environmental enrichment attenuates cognitive deficits, but does not alter neurotrophin gene expression in the hippocampus following lateral fluid percussion brain injury. Neuroscience. 2002;112:631–7.
21. Ronnback A, Dahlqvist P, Svensson PA, et al. Gene expression profiling of the rat hippocampus one month after focal cerebral ischemia followed by enriched environment. Neurosci Lett. 2005;385:173–8.
22. Kolb B, Gibb R. Environmental enrichment and cortical injury: behavioral and anatomical consequences of frontal cortex lesions. Cereb Cortex. 1991;1:189–98.
23. Passineau MJ, Green EJ, Dietrich WD. Therapeutic effects of environmental enrichment on cognitive function and tissue integrity following severe traumatic brain injury in rats. Exp Neurol. 2001;168:373–84.
24. Nithianantharajah J, Hannan AJ. Enriched environments, experienced dependent plasticity and disorders of the nervous system. Nat Rev Neurosci. 2006;7(9):697–709.

25. LeWinn EB, Dimancescu MD. Environmental deprivation and enrichment in coma. Lancet. 1978;2:156–7.
26. Lombardi F, Taricco M, De Tanti A, et al. Sensory stimulation of brain-injured individuals in coma or vegetative state: results of a Cochrane systematic review. Clin Rehabil. 2002;16:464–72.
27. Doman G, Wilkinson R, Dimancescu M, et al. The effects of intense multi-sensory stimulation on coma arousal and recovery. Neuropsychol Rehabil. 1993;3(2):203–12.
28. Wood RL. Critical analysis of the concept of sensory stimulation for patients in vegetative states. Brain Inj. 1991;5:401–9.
29. Jones R, Hux K, Morton-Anderson K, et al. Auditory stimulation effect on a comatose survivor of traumatic brain injury. Arch Phys Med Rehabil. 1994;75(2):164–71.
30. Blackerly WF. Intensity of rehabilitation and length of stay. Brain Inj. 1990;4(2):167–73.
31. Hall M, MacDonald S, Young G. The effectiveness of directed multisensory stimulation versus non directed stimulation in comatose closed head injured patients: pilot study of a single subject design. Brain Inj. 1992;6(5):435–45.
32. Lippert-Grüner M, Terhaag D. Multimodal early onset stimulation (MEOS) in rehabilitation after brain injury. Brain Inj. 2000;14(6):585–94.
33. Mitchell S, Bradley V, Welch J, et al. Coma arousal procedure: a therapeutic intervention in the treatment of head injury. Brain Inj. 1990;4(3):273–9.
34. Sisson R. Effects of auditory stimuli on comatose patients with head injury. Heart Lung. 1990;19(4):373–8.
35. Tablot L, Whitaker H. Brain-injured persons in an altered state of consciousness: measures and intervention strategies. Brain Inj. 1994;8(8):689–99.
36. Wilson S, Powell G, Elliott K, et al. Sensory stimulation in prolonged coma: four single case studies. Brain Inj. 1991;5(4):393–400.
37. Wilson S, Powell G, Brock D, et al. Behavioural differences between patients who emerged from vegetative state and those who did not. Brain Inj. 1996;10(7):509–16.
38. Johnson D, Roethig-Johnston K, Richards D. Biochemical and physiological parameters of recovery in acute severe head injury: responses to multisensory stimulation. Brain Inj. 1993;7(6):491–9.
39. Kater K. Response of head-injured patients to sensory stimulation. Western J Nurs Res. 1989;11:20–33.
40. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. Lancet. 1974;2(7872):81–4.
41. Davis A, Gimenez A. Cognitive-behavioral recovery in comatose patients following auditory sensory stimulation. J Neurosci Nurs. 2003;35(4):202–9.
42. Urbenjaphol P, Jitpanya C, Khaoropthu S. Effects of the sensory stimulation program on recovery in unconscious patients with traumatic brain injury. J Neurosci Nurs. 2009;41:10–6.
43. Oh H, Seo W. Sensory stimulation programme to improve recovery in comatose patients. Clin Nurs. 2003;12:394–404.
44. Di Stefano C, Cortesi A, Masotti S, et al. Increased behavioural responsiveness with complex stimulation in VS and MCS: preliminary results. Brain Inj. 2012;26(10):1250–6.
45. Lotze M, Schertel K, Birbaumer N, et al. A long-term intensive behavioral treatment study in patients with persistent vegetative state or minimally conscious state. J Rehabil Med. 2011;43(3):230–6.
46. Pape TL, Rosenow JM, Steiner M, et al. Placebo-controlled trial of familiar auditory sensory training for acute severe traumatic brain injury: a preliminary report. Neurorehabil Neural Repair. 2015;29(6):537–47.
47. Castro M, Tillmann B, Luauté J, et al. Boosting cognition with music in patients with disorders of consciousness. Neurorehabil Neural Repair. 2015;29(8):734–42. doi:10.1177/1545968314565464.
48. Peck KJ, Girard TA, Russo FA, et al. Music and memory in Alzheimer's disease and the potential underlying mechanisms. J Alzheimers Dis. 2016;51(4):949–59.

49. Bloem BR, de Vries NM, Ebersbach G. Nonpharmacological treatments for patients with Parkinson's disease. Mov Disord. 2015;30(11):1504–20.
50. Geretsegger M, Elefant C, Mössler KA, et al. Music therapy for people with autism spectrum disorder. Cochrane Database Syst Rev. 2014;(6):CD004381.
51. François C, Grau-Sánchez J, Duarte E, et al. Musical training as an alternative and effective method for neuro-education and neuro-rehabilitation. Front Psychol. 2015;6:475.
52. O'Kelly J, James L, Palaniappan R, et al. Neurophysiological and behavioural responses to music therapy in vegetative and minimally conscious states. Front Hum Neurosci. 2013;7:884.
53. Lichtensztejn M, Macchi P, Lischinsky A. Music therapy and disorders of consciousness: providing clinical data for differential diagnosis between vegetative state and minimally conscious state from music-centered music therapy and neuroscience perspectives. Music Ther Perspect. 2014;32(1):47–55.
54. Perrin F, Castor M, Tillmann B, et al. Prooting the use of personally relevant stimuli for investigating patients with disorders of consciousness. Front Psychol. 2015;6:1102.
55. Bradt J, Magee WL, Dileo C, et al. Music therapy for acquired brain injury. Cochrane Database Syst Rev. 2010;7:CD006787.
56. Magee WL, O'Kelly J. Music therapy with disorders of consciousness: current evidence and emergent evidence-based practice. Ann N Y Acad Sci. 2015;1337:256–62.
57. Schiff ND, Giacino JT, Kalmar K, et al. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. Nature. 2007;448(7153):600–3.
58. Thibaut A, Bruno MA, Ledoux D, et al. tDCS in patients with disorders of consciousness: sham-controlled randomized double-blind study. Neurology. 2014;82(13):1112–8.

Chapter 11
Pharmacological Treatments

Olivia Gosseries and John Whyte

Abstract We review the current state of knowledge of potentially useful drugs acting on the recovery of consciousness in severely brain-damaged patients. Exploratory and retrospective studies as well as case reports on the sporadic cases of recovery are discussed regarding pharmacological treatments such as amantadine, levodopa, bromocriptine, apomorphine, methylphenidate, zolpidem, baclofen, and lamotrigine. Potential underlying mechanisms explaining the effects of these drugs on the awakening and recovery of consciousness in this challenging population are also examined. Finally, we discuss the process of using single-subject methods to assess the off-label use of a specific medication.

Introduction

Disorders of consciousness (DOC) resulting from a severe brain injury include coma [1], the unresponsive wakefulness syndrome (UWS, vegetative state) [2, 3] and the minimally conscious state (MCS) [4]. There are currently only a very few evidence-based guidelines regarding the treatment of patients with DOC. Studies showed that some severely brain-damaged patients benefit from pharmacological treatments, brain stimulation techniques, rehabilitation, and/or sensory stimulation therapies; but, in general, responses to treatment still remain unsatisfactory [5–8]. By targeting various pathways of the central nervous system, several pharmacological agents can contribute to the recovery of consciousness in some patients. Sensory perception is

O. Gosseries, Ph.D. (✉)
Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium

Department of Psychiatry, University of Wisconsin, Madison, WI, USA
e-mail: ogosseries@ulg.ac.be

J. Whyte, M.D., Ph.D.
Moss Rehabilitation Research Institute and MossRehab, Elkins Park, PA, USA
e-mail: jwhyte@einstein.edu

C. Schnakers, S. Laureys (eds.), *Coma and Disorders of Consciousness*,
DOI 10.1007/978-3-319-55964-3_11

controlled by a complex neural network, which includes reticulothalamic cholinergic projections and thalamocortical and reticulocortical glutaminergic projections. Lesions in the white matter connections of these networks may affect consciousness and cognition [9], and several drugs including dopaminergic agents can act on this network and support recovery of consciousness.

Using psychoactive medications to enhance cognitive and behavioral performance is challenging for several reasons. The mechanisms of psychoactive drugs are characterized by the types of receptors they activate or the neurotransmitters or ion transport processes they modulate. In contrast, the goals of treatment are to alter specific cognitive processes such as arousal, memory or behavioral phenomena such as aggression or initiation of functional activities. Unfortunately, there is no simple correspondence between these two levels of analysis. If a drug affects a system that is relevant to our clinical goals, we can be sure it also affects other systems that we might not choose to manipulate. Thus, the decision to administer a psychoactive drug typically requires one or more implicit or explicit hypotheses: "This drug binds to receptor class X. Activation of receptor class X is thought to enhance arousal. I hypothesize that increased arousal in this patient will enhance the reliability of command following." This is the motivation for trying the drug. But it may be that activation of receptor class X has a number of other effects that are negative and outweigh its value for enhancing arousal. Moreover, even if we successfully enhance arousal, it might be that the patient's command following is primarily limited by apraxia rather than lack of arousal, and therefore command following may not result even if arousal is successfully enhanced.

Another challenge is the gap between the words we use to describe psychological and behavioral constructs and our growing knowledge of the complex and interactive nature of the brain. We have one word for "arousal," but we know that arousal is affected by at least four different neurotransmitters, and we have come to understand that some have greater effects on "readiness to detect" and others on "readiness to act" [10, 11]. So saying that we want to enhance a patient's arousal, itself, is too crude a statement.

Finally, psychoactive drugs ultimately act on some specific biological target, and to be beneficial, the patient must have that target available. A drug that stimulates the release of a natively produced neurotransmitter or which prolongs its presence in the synapse cannot be effective unless there is sufficient endogenous production of that neurotransmitter. A direct agonist of postsynaptic receptors cannot be effective unless there are sufficient downstream neurons to respond to that agonist. Thus, we hypothesize that there are particular patterns of neural network damage and preservation that may predict whether a patient can respond to the drug, though at present we are far from being able to define these patterns and use them in treatment selection.

This chapter will summarize the current state of the art on potentially useful drugs, such as amantadine, levodopa, bromocriptine, apomorphine, methylphenidate, zolpidem, baclofen, and lamotrigine, that can act on the recovery of consciousness in DOC patients. Recent neuroimaging studies on the effect of pharmacological treatments will be discussed, and we will explore some potential underlying mechanisms

explaining the effects of these drugs on the recovery of consciousness. We will also comment on the process of using individual subject methods to investigate the off-label use of other medications that have not yet been adequately studied.

Potential Pharmacological Treatments

Amantadine

Amantadine is an old dopaminergic agent initially used in the treatment of Parkinson's disease. It was also employed against influenza due to its antiviral properties, but due to the frequent mutations of the virus and to the advent of new drugs, it is no longer recommended as an antiviral drug. Amantadine increases the availability of dopamine in the striatum both at the pre- and postsynaptic levels. It facilitates the release of dopamine and delays its reuptake, resulting in an increase of synaptic dopamine concentration [9]. At the postsynaptic level, amantadine increases the number of dopaminergic receptors [12]. It is also a dose-dependent antagonist of the *N*-methyl-D-aspartate receptors.

The use of amantadine is correlated with a better outcome among severe traumatic brain-injured patients [13–15]. A retrospective study has shown that in 74 acute traumatic patients diagnosed in UWS, the group treated with amantadine obtained higher scores on the Glasgow Coma Scale (GCS) [16] than the group who did not receive the drug when discharged from the intensive care unit [13]. Mortality was also lower in the treatment group than in the non-treatment group. Another study on 35 patients showed a higher functional improvement, as assessed with the Mini-Mental State Examination [MMSE] [17], the Glasgow Outcome Scale [18], and the Disability Rating Scale [DRS] [19], during a treatment of over 6 weeks in the acute phase of severe traumatic brain injury [20]. Similarly, Whyte et al. showed that patients with traumatic etiology receiving amantadine had better DRS scores 4 months postinjury than those who did not receive the treatment [14]. Note that these studies took place when patients were still in the acute or subacute stage and, thus, they do not provide information on patients with a slower recovery process or with chronic DOC and could potentially be biased by early spontaneous recovery.

Zafonte et al. reported a dose-dependent response to amantadine in one MCS patient examined 5 months after a brain trauma. During the treatment, the patient recovered his communication abilities, and the score on the Coma/Near-Coma (CNC) scale [21] increased. This effect was reversible when the treatment was stopped; and during its reintroduction, the patient could communicate again [22]. Another recent case report of a non-traumatic MCS patient also showed a dose-dependent response to amantadine, but when the dosage was increased to 200 mg per day, the patient presented unexplained tachycardia [23].

A well-designed controlled multicenter study has recently been conducted by Giacino and Whyte et al. that has so far the highest level of evidence for the use of

amantadine in promoting recovery of consciousness in patients with DOC [24]. This double-blind, randomized, placebo-controlled trial of a 6-week duration study assessed 184 patients who were either in UWS or MCS 1–4 months after traumatic brain injuries. Patients were randomly assigned to receive amantadine or placebo treatment for 1 month and were followed for 2 weeks after the treatment was discontinued. In keeping with evidence from the rate of change during inpatient rehabilitation (i.e., due to spontaneous recovery or stimulation programs), both groups had improved during the 1-month period. Nonetheless, functional recovery (e.g., recovery of consistent response to commands, intelligible verbalization, reliable yes-no communication, functional use of objects) was faster in the amantadine group than in the placebo group, as measured by the improved DRS scores. Although improvements were generally maintained in the amantadine group after the washout period, the rate of functional recovery attenuated after stopping the treatment, and DRS scores were converging between the amantadine and placebo groups at the 6-week follow-up assessment (Fig. 11.1). These results suggest that amantadine accelerated the pace of functional recovery during active treatment in patients with DOC when assessed in the acute and subacute settings. Note that exposure to amantadine did not increase the risk of adverse events (e.g., seizures).

Most of the aforementioned studies only involved patients with traumatic brain injury. A recent retrospective study on non-traumatic etiologies explored the effect

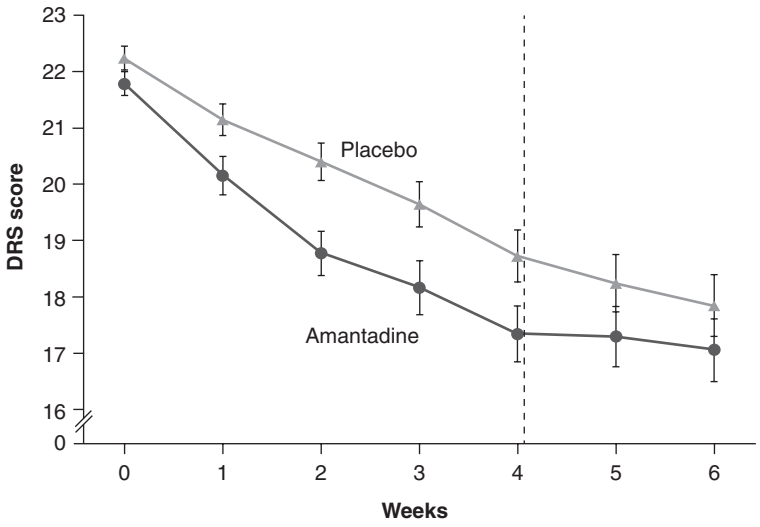

Fig. 11.1 Behavioral results of amantadine treatment as compared to placebo during a 6-week assessment period. DRS scores range from 0 to 29 with higher scores indicating more severe functional disability. DRS scores improved faster in the amantadine group than in the placebo group during the 4-week treatment period. During the washout period (the last 2 weeks), the rate of recovery was slower in the amantadine group, and mean DRS scores were similar for the two groups at the 6-week mark. The bars denote the standard error (Taken from [24])

of amantadine and methylphenidate in patients resuscitated after a cardiac arrest [25]. Out of a cohort of 588 acute patients, 16 patients received amantadine, methylphenidate, or a combination of both. Compared to the control group, patients receiving neurostimulants trended toward an increased frequency of goal-directed behaviors at the bedside (i.e., command following) with an improved distribution of the Cerebral Performance Category scale and modified Rankin scale scores. These patients also showed a higher survival rate after hospital discharge. Even if this study suggests a potential therapeutic option for post-cardiac arrest patients in acute setting, it does not account for the spontaneous recovery bias. A controlled prospective trial is still needed to fully determine the effect of amantadine in pathologies other than brain trauma.

Finally, to date, only three studies used electrophysiology or neuroimaging techniques to gather objective information about the amantadine efficacy in DOC patients. A first study used electroencephalogram (EEG) to show an increase of alpha activity and a decrease of theta activity in one UWS patient who clinically responded to amantadine [26]. A second case report of a non-traumatic MCS patient showed that during amantadine treatment when the patient was able to communicate and use objects (i.e., emergence of MCS), the EEG data also showed an increase in predominant background alpha activity (10–11 Hz), while during baseline and washout periods, the EEG showed moderately abnormal EEG background (7–8 Hz) [27]. Note that this case also presented a dose-dependent effect, but epileptic facial myoclonus was observed during treatment, which led to the discontinuation of amantadine. The third study conducted by Schnakers et al. used fluorodeoxyglucose positron emission tomography in an ABAB paradigm in a post-anoxic chronic MCS state who responded to amantadine [28]. Behaviorally, the patient improved at the motor level and responded to verbal commands after amantadine treatment. The scores at the Coma Recovery Scale-Revised (CRS-R [29]) also increased substantially. Metabolically, amantadine-related increases in brain activity were measured in the fronto-temporoparietal network and in sensorimotor areas. These brain regions were previously hypometabolic when compared to healthy subjects' scans, and their metabolism increased after 5 weeks of treatment, decreased after withdrawal, and resumed near-normal values after amantadine reintroduction (Fig. 11.2).

In conclusion, amantadine seems to be a suitable medication to promote recovery of consciousness in patients with traumatic DOC, as well as other cognitive functions related to arousal and memory [30], but its effects in non-traumatic DOC are less clear. It can be started days to months post-injury and still produce benefits. Amantadine has a quick onset of action with functional results observed within the first 4 weeks of administration. The administered dosage varies between 100 and 400 mg daily in adults (average of 200 mg a day). A few side effects have been reported so far, mostly in case report studies, ranging from mild to severe. More neurophysiological and neuroimaging studies are also needed to better understand the underlying mechanisms of the positive effect of amantadine in patients with DOC.

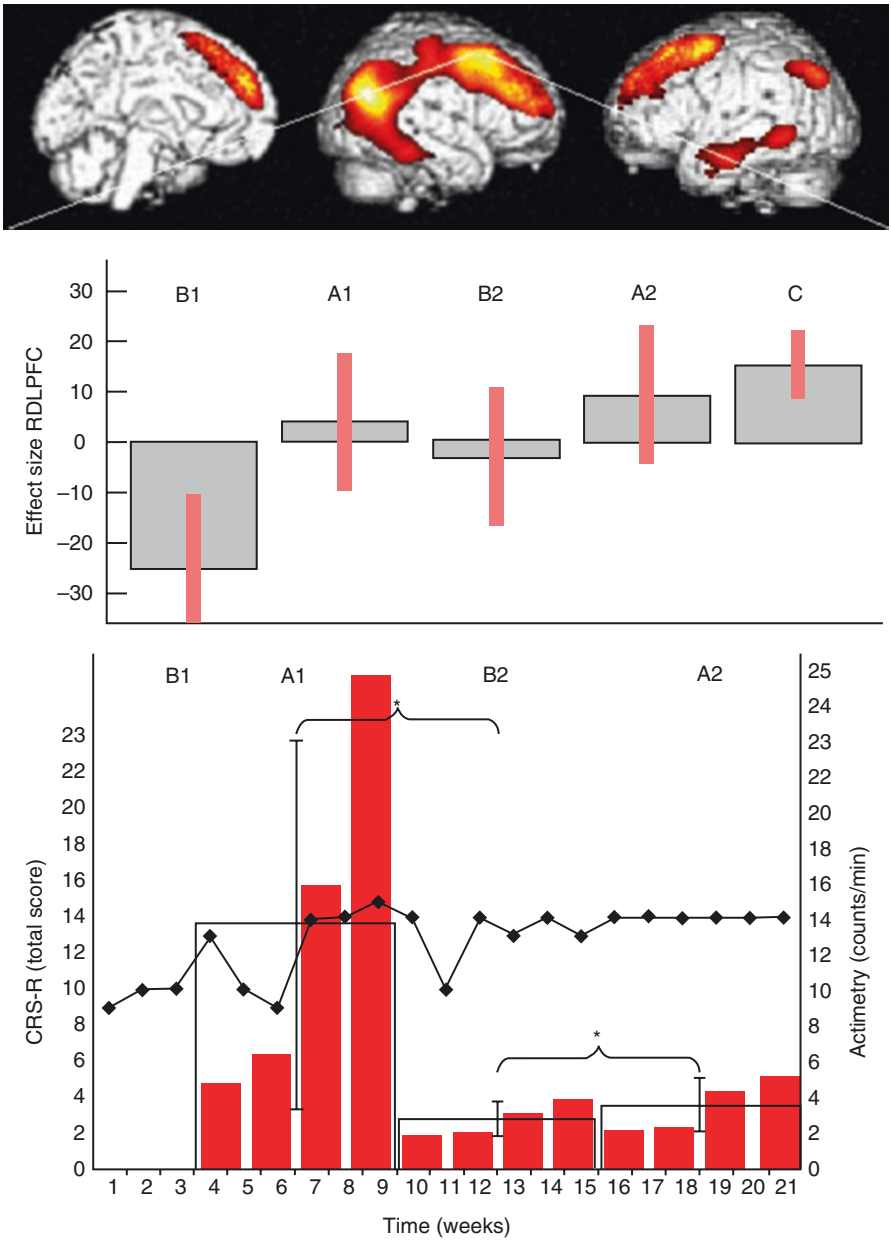

Fig. 11.2 Behavioral and metabolic effect of amantadine in one anoxic MCS patient. *Upper panel*: ABAB design showing treatment-related metabolic changes compared with healthy controls (C) in widespread bilateral fronto-temporo-parietal associative and right-sided sensorimotor areas. *Lower panel*: behavioral changes as assessed by the CRS-R total score during 21 weeks (*black diamonds*). Actimetry monitoring is represented as mean motor activity counted per week (*red bars*) or per month (*white bars*). *Asterisks* represent the significant difference of motor activity between conditions (B1 > A2 < B2). RDLPFC, right dorsolateral prefrontal cortex (Taken from [28])

Levodopa

As amantadine, levodopa is a dopaminergic agent initially indicated in the treatment of Parkinson's disease. Remarkable recovery was observed in the 1990s in a 24-year-old man diagnosed with traumatic UWS for 6 months, who was able to speak a few days after the administration of levodopa [31]. Note that standardized validated diagnostic behavioral assessment was not used in this case and it was published before the introduction of the criteria of the MCS in 2002, and thus the initial diagnosis of UWS might have been inaccurate. Five other DOC patients with traumatic lesions also became more responsive after taking levodopa, which was initially given to treat extrapyramidal signs [32, 33]. In another uncontrolled unblinded study, eight UWS patients recovered signs of consciousness after the administration of progressive amounts of levodopa. All patients responded to commands within the first 2 weeks of treatment, and seven of them (including two assessed more than 9 months post-injury) were able to interact in a functional way [34]. Finally, in a last prospective case series, some remarkable responses to L-dopa/carbidopa were observed in 9 out of 11 traumatic and non-traumatic UWS patients. The effects were observed within 10 days of treatment (275 mg/day) and included the recovery of command following and reciprocal interaction. The authors suggested that the behavioral improvement was due to the treatment itself and not to the spontaneous recovery because the time since injury was between 30 and 180 days, and patients were in a UWS for at least 1 month without any improvement before being included in the trial [35]. Nevertheless, none of these studies formally controlled for natural recovery.

Bromocriptine

Bromocriptine is another dopamine agonist used primarily to treat Parkinson's disease. This agent, less studied, is mainly an agonist of the postsynaptic dopamine D2 receptors. It has been associated with a higher rate of patients recovering from a posttraumatic UWS in a retrospective study [36]. However, in a 6-week double-blind, placebo-controlled, crossover study, bromocriptine (5 mg twice daily) did not improve attentional skills in 12 conscious patients with moderate-to-severe traumatic brain injury [37]. Moreover, it possibly induced negative side effects (e.g., dizziness) in some patients.

Apomorphine

Apomorphine is a nonselective dopaminergic agonist, which activates D1 and D2 receptors with a preference for the latter [38]. This therapy was initially indicated to treat Parkinson's disease and erectile dysfunction but it has also shown positive effects in a few severe brain-injured patients. An MCS patient treated with

apomorphine 104 days after a brain trauma suddenly recovered consciousness after 1 day of treatment. He was able to move his legs upon request and to answer yes-no questions, which was not the case before [39]. After stopping the treatment, the patient remained fully conscious, and a considerable functional recovery was still maintained. Diffusion tensor imaging showed a reduction in thalamocortical and corticothalamic projections, as expected in such patients [40]. Another uncontrolled case study of eight UWS and MCS patients with traumatic etiology who were treated continuously with apomorphine showed a recovery of consciousness for all patients except one, with an improvement in CNC and DRS scores [41]. These improvements lasted for at least 1 year, even after stopping the treatment. As above, the design used in these two studies does not distinguish between improvements induced by apomorphine and ones that could have occurred spontaneously.

More studies in DOC patients are needed to confirm the potential benefit of apomorphine (but also levodopa and bromocriptine) using double-blind placebo-controlled designs and, if possible, complement these with neuroimaging techniques.

Methylphenidate

This neurostimulant was initially used for children presenting attention-deficit hyperactivity disorders, and it was also prescribed for narcoleptic patients. This agent increases the release of dopamine and noradrenalin while blocking their reuptake and inhibiting monoamine oxidase, which increases noradrenergic activity in the striatum and other brain areas such as the caudate nucleus and the medial frontal cortex [9].

Only a few studies using methylphenidate have been conducted in DOC patients to improve the level of consciousness. One study suggested that the early use of methylphenidate in intensive care is associated with shorter hospital stays after severe trauma [42]. In a retrospective study, comatose post-cardiac arrest patients receiving neurostimulants trended toward improved rate of following commands, survival to hospital discharge, and increases at several behavioral scales [25]. Another study including 14 patients with impaired consciousness after acquired brain injury reported improvement in GCS scores after methylphenidate administration. This behavioral amelioration was mainly associated with increased cerebral glucose metabolism in the posteromedial parietal cortex, suggesting that this brain area, which is part of the neural network for consciousness, may be the relevant structure for the pharmacological response to methylphenidate treatment in DOC patients [43]. On the other hand, a meta-analysis of command following and communication activity in 22 chronic patients with DOC (17 of traumatic etiology) did not show any clinical improvement on the percentage of responses to command after the administration of methylphenidate [44].

Methylphenidate has mostly been studied for its positive effect on attention and memory in the acute and subacute phases of recovery in patients suffering from moderate to severe brain injury [45–49]. More recently, methylphenidate has been associated with a global reduction of cerebral blood flow and a decreased activity in the left posterior superior parietal cortex and parieto-occipital junction during task performance. This finding suggests a compensatory mechanism by which the drug ameliorates attention impairments in traumatic brain-injured patients [49].

Finally, ten children and teenagers in a UWS and MCS were treated with a combination of dopaminergic drugs (amantadine, methylphenidate, bromocriptine, levodopa, pramipexole) and improved their responses to structured stimuli in an uncontrolled, unblinded prospective study [50].

Zolpidem

Zolpidem is an imidazopyridine which acts like an agonist on subtype 1 of the inhibiting receptors of the gamma-aminobutyric acid ($GABA_A$). This agent was initially recommended in the treatment of insomnia and presents sedative, anticonvulsive, anxiolytic, and myorelaxant effects.

Many studies have now reported the use of zolpidem as an "awakening" agent among UWS and MCS patients. This drug produces, occasionally, a clear paradoxical temporary effect on the level of consciousness in patients with severe brain damage. The effect of zolpidem was described for the first time in 2000 after the fortuitous discovery in an allegedly UWS patient who had had a traumatic brain injury 3 years earlier and who started to communicate 20 min after the administration of the medication [51]. Clauss and colleagues subsequently reported impressive effects of this drug in four other UWS patients who had suffered a traumatic or anoxic cerebral lesion 3–5 years before [52]. Patients were able to answer questions, speak, and feed themselves shortly after taking a single dose of zolpidem (10 mg). Improvements were also observed at the GCS scale and the Rancho Los Amigos scale [53]. The level of consciousness of these patients returned to its initial state 4 h after the administration of the drug, but an improvement was observed again at the time of readministration. Similar transitory effects have also been reported among patients in MCS resulting from cerebral anoxia or encephalitis [54–57]. Some case studies underlined, however, the absence of improvement among other patients suffering from post-anoxic encephalopathy or severe brain trauma [58–60].

The percentage of responders has recently been investigated among patients in UWS and MCS. The first preliminary study showed that among 15 patients, only one indicated a significant clinical response transitioning from UWS to MCS. The remaining 14 patients did not show any improvement [60]. In a subsequent placebo-controlled double-blind crossover study, among 84 DOC patients of at least 4-month duration, only four showed significant recovery such as increased movement, social interaction, command following, and functional object use [61]. The effect typically lasted 1 or 2 h, and mild adverse events occurred in some patients (e.g., shaking or

restless movements). Thus, in these two studies, around 5% of the participants responded to zolpidem, and the responders could not be distinguished in advance from the nonresponders.

An EEG study in a single post-stroke chronic UWS patient showed that zolpidem could produce less dramatic changes than the ones previously reported [62]. For instance, after zolpidem, the patient could open her eyes sustainably and start yawning, which was correlated with activation of EEG cortical activity [63]. Thus, although zolpidem may produce rapid and dramatic improvements in a few cases, its effects are subtle or absent in most patients. Along the same lines, a clinical trial in 60 chronic patients with DOC showed that only one MCS patient showed behavioral improvements (i.e., functional use of objects) [64]. However, following this performance, the patient was then reassessed in a double-blind placebo-controlled trial but failed to show any clinical improvement. Four other patients showed increased total scores at the CRS-R after zolpidem intake that were never observed before, suggesting that the drug can induce inconsistent effects.

To assess the efficacy of zolpidem treatment according to the patients' site of injury, 127 subacute patients in UWS were evaluated over a 1-week daily treatment. Patients were divided into two non-brainstem injury (i.e., brain countercoup contusion and brain compression injury) and two brainstem injury groups (i.e., primary and secondary brainstem injuries). Under zolpidem, the level of consciousness of the non-brainstem injury groups was better than before treatment, whereas no changes were observed for the brainstem injury groups. SPECT measures also showed increased perfusion in brain-damaged areas in the non-brainstem injury groups, while no changes could be observed in the brainstem groups. These findings suggest positive effects of zolpidem on brain functions only in the absence of brainstem injuries [65].

Several studies were interested in the mechanisms that could explain the effect of zolpidem. Single-photon emission computed tomography studies showed that zolpidem increases the cerebral metabolism of hypoactive areas following traumatic or anoxic lesions [51, 52, 66]. In the same line, using PET scan in one MCS patient, improvement of neuropsychological performances was correlated with an increase in cerebral metabolism in the frontal and postrolandic areas after zolpidem intake. Activations were also observed in anterior cingulate and orbitofrontal cortex, areas known to be involved in motivational processes [54]. Using resting state fMRI in a single post-stroke chronic UWS patient who showed minimal improvement after zolpidem (see above, [62]), increased BOLD signal was transiently measured in a widely distributed cortico-subcortical network (i.e., frontal cortices, anterior cingulated areas, thalamus and caudate nucleus). In comparison, a healthy participant showed a deactivation of the frontal, parietal, and temporal cortices after zolpidem administration. Those BOLD signal changes in the UWS patient also correlated with concentrations of extravascular metabolites in the frontal cortex. These findings suggest a zolpidem-induced modulation of neurometabolism with an increased metabolism related to a dormancy switch-off in a widespread frontoparietal network [67]. Consistently, another PET study showed metabolic level increases after zolpidem intake in a set of hypoactive areas encompassing the limbic loops (i.e., orbitofrontal

cortex) in three chronic postanoxic MCS patients [68] (Fig. 11.3a). All patients recovered functional communication after administration of zolpidem, and none of them presented structural lesions on the brain areas showing increased metabolism after zolpidem. Additionally, zolpidem responders also seemed to present an increase in EEG power at ~15–30 Hz associated with an attenuation of ~6–10 Hz power after the zolpidem intake [69] (Fig. 11.3b). Another recent chronic post-anoxic UWS case report showed an increase of amplitude and voltage with a theta-beta rhythm over temporal areas along with an increase of CRS-R score during higher dosage of zolpidem (30 mg instead of 10 mg) without relevant side effects [70].

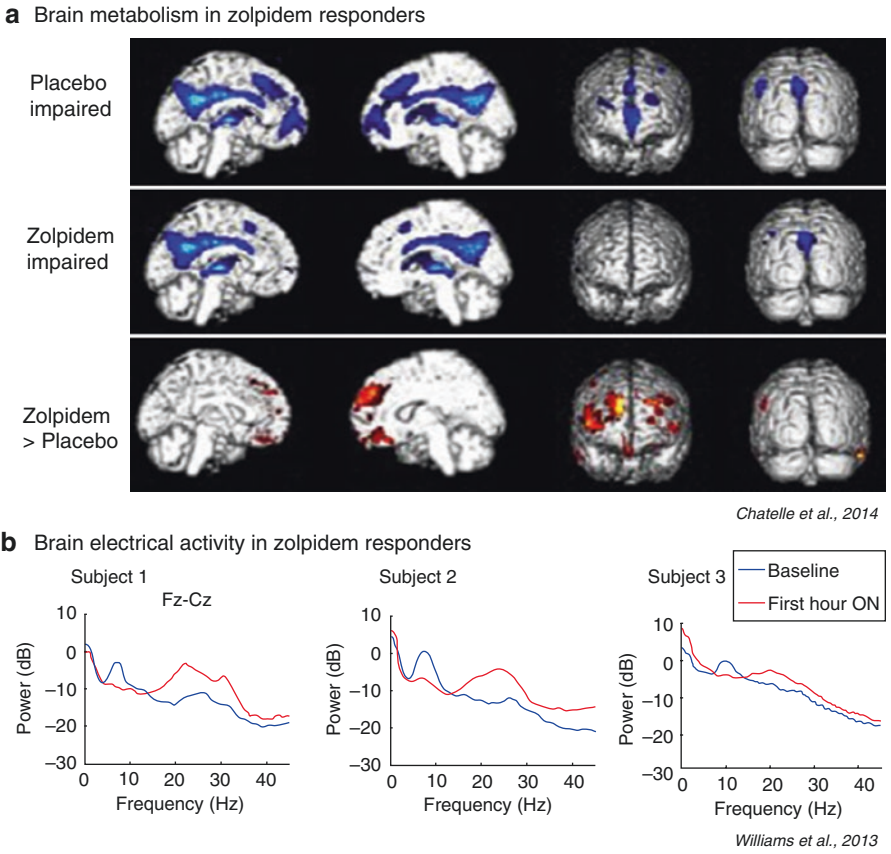

Fig. 11.3 Neuroimaging and neurophysiology of zolpidem responders. (**a**) Brain metabolism assessed with PET scan. *Blue areas* show decreased brain metabolism after placebo and after zolpidem intake, and *red brain areas* show recovery after zolpidem in three MCS patients. (**b**) Brain electrical activity assessed with EEG. Power spectra measured from midline EEG channel Fz-Cz recordings from three MCS patients. The average spectral power in the hour prior zolpidem dose is shown in *red* and in *blue* the average spectral power in the 20–60 min after the zolpidem dose (Taken from [68, 69])

A mechanism of cell dormancy was proposed to explain the effect of zolpidem: certain nonspecific areas of the brain, adjacent or distant to the initially damaged zones (e.g., the ipsilateral and contralateral hemisphere or the cerebellum), might be inhibited by the lesion. These inactive parts of the brain would recover their function after taking zolpidem, generating a recovery of consciousness [51, 54, 66, 71]. In line with this hypothesis, a study using magnetoencephalography showed that zolpidem decreased the number of pathological slow waves associated to dormant cerebral tissue in a patient who had a stroke [72].

From a molecular point of view, changes could take place at the level of glutamate and GABA neurotransmitters close to the cerebral lesions. The release of glutamate produces an excitotoxicity and an excess of inhibitory GABA neurotransmitters as well as a long-term oversensitiveness of the $GABA_A$ receptors [51, 52]. The inhibitory neurotransmitters, while binding to the receptors of the ionic channels, generate a reduction of metabolism and blood flow in the adjacent cerebral areas, thus causing a state of cell dormancy. While binding to $GABA_A$ receptors of dormant cells, zolpidem provokes the inversion of the abnormal state of the neurons and associated metabolic inhibition. The "GABA impairment hypothesis" was thus proposed to explain the effect of zolpidem on recovery of consciousness, which states that zolpidem may act on the recovery of consciousness by reversing the impairment of GABA and, hence, by restoring normal ratio between synaptic excitation and inhibition [73]. According to the mesocircuit model (see below), zolpidem could interact with the limbic loops of the brain and modulate subcortical connections, more particularly the globus pallidus, which would bring the thalamocortical activity back to normal and would allow a recovery of consciousness [74].

In conclusion, zolpidem responders are rare, i.e., around 5% of UWS and MCS patients from both traumatic and non-traumatic etiology. The dosage varies among studies, but the standard dose is 10 mg with an effect that lasts a few hours. Several hypotheses have been proposed regarding the underlying mechanism of zolpidem paradoxical responses, but future research is still needed to better understand the mechanism of zolpidem in enhancing consciousness and to identify biomarkers that can predict a clinically meaningful treatment response.

Baclofen

Baclofen is an agonist agent of the $GABA_B$ receptors, which acts on the posterior horn of the spinal cord and which is used mainly against spasticity. This symptom is frequently observed after central nervous system lesions and can limit voluntary movements in patients with DOC. The antispasmodic effect of baclofen remains modest when it is administered orally. A direct and continuous perfusion of baclofen in low doses in the cerebrospinal fluid is more effective. Intrathecal baclofen therapy can be a useful treatment against severe spasticity among DOC patients, which improves the quality of life by reducing pain-related spasms and contracture

formation [75]. It can also help control persistent autonomic dysfunctions such as tachycardia, tachypnea, fever, and breathing difficulties [76].

In uncontrolled case studies, some impressive cases of recovery were reported in UWS patients who were treated with baclofen in the subacute setting [77–79]. A positive effect of baclofen was also observed in five UWS patients treated for spasticity in the chronic stage (at least 19 months post-injury). Two weeks after the start of the treatment, all except one patient presented clinical improvement, which remained stable until the end of the 6-month follow-up interval [80]. Improvements went from an increase in vigilance to a recovery of consciousness, as revealed by changes in CRS-R scores. Similarly, two traumatic MCS patients with spasticity received intrathecal baclofen and emerged from the MCS, but their cognitive deficits remained severe [81]. In another recent prospective study, two out of eight DOC patients that had spasticity showed a marked and sustained improvement after intrathecal baclofen therapy, and they emerged from MCS [82]. Long-term outcome (10-year follow-up) has also been studied in a cohort of 53 severe traumatic or hypoxic patients treated with intrathecal baclofen. A good functional recovery occurred in the traumatic group but not in the hypoxic group, which suggests that hypoxic patients tend to be less responsive to the baclofen treatment than traumatic patients [83]. Among the traumatic group, 21% patients died, 30% patients were severely disabled or in a UWS, and 49% had good recovery of consciousness. Patients who had a good recovery tended to receive baclofen later, and they needed lower doses of baclofen, while poor long-term outcome was associated with early development of severe symptoms of dysautonomia associated with hypertonia [84].

Several assumptions have been made to explain the effects of baclofen on recovery of consciousness. Some authors suggest a modulation of motor impulses of the spinal cord on possible cortical reactivation [80]. By improving nervous conduction in the demyelinated axons, Baclofen could possibly accelerate the repair of diffuse axonal injury [85]. It has also been hypothesized that intrathecal baclofen therapy may act by reducing the overload of dysfunctional sensory stimuli reaching the injured brain [75]. A modulation of the sleep-wake cycle has also been considered as a mechanism responsible for the effect of baclofen [80]. However, as in many of the medications discussed above, studies of baclofen which adequately control for natural recovery are lacking.

Lamotrigine

Lamotrigine is an agent used in the treatment of epilepsy and bipolar disorders. By inhibiting the voltage-dependent sodium channels, it stabilizes the neuronal membrane and inhibits glutamate release. Its effects on the sodium ion channels contribute to the antiepileptic effects, while the antiglutamatergic agents act more on the psychotropic effects with a possible neuroprotective action [86, 87]. Functional improvement of patients with severe brain injuries has been observed in only one study after administration of lamotrigine, which showed recovery of consciousness

and cognition combined with an earlier discharge from hospital [88]. This uncontrolled unblinded study suggested a possible effect on functional recovery, particularly in patients who had spontaneously emerged from the MCS. This medication might influence other aspects of cognitive performance than the level of consciousness per se [89].

Mechanisms Aiming to Explain the Possible Positive Effects of Pharmacological Treatments

Each drug affects one or more neuronal pathways. Amantadine, levodopa, bromocriptine, methylphenidate, and apomorphine act mainly on the dopaminergic system, whereas zolpidem and baclofen affect preferentially the GABAergic system (albeit at different locations in the nervous system). The subjacent neurological mechanisms to the positive effects of these drugs are currently not well understood. As we have seen, amantadine and zolpidem would increase the metabolism of hypoactive cerebral regions [28, 90]. Zolpidem would play a main role in the GABAergic system of the limbic loops in the brain [90], whereas baclofen would act more on the spinal cord and might support the regeneration of motor neurons [80].

More specifically, the favorable effect of dopaminergic agents on arousal and awareness in patients with DOC may reflect enhanced neurotransmission in the dopamine-dependent nigrostriatal, mesolimbic, mesocortical, and/or thalamic pathways (Fig. 11.4) [91, 92]. These pathways mainly originate in the brainstem and project forward to interact with different structures of the midbrain and cerebral cortex. The nigrostriatal pathway, which starts in the substantia nigra and ends in the basal ganglia or striatum, plays a major role in behavior initiation and motor functions. The mesolimbic pathway, which projects from the midbrain ventral tegmental area to the nucleus accumbens in the ventral striatum, is associated with emotional processes, motivation, learning, and memory. The mesocortical circuit, encompassing excitatory projections from the ventral tegmental area to the prefrontal cortex, is believed to be involved in cognition and executive function (via the dorsolateral prefrontal cortex) as well as in emotions and affect (via the ventromedial parts of the prefrontal cortex) [91, 92]. In addition to these three pathways, another system including the thalamus is important for mediating arousal and awareness and hence might play a key role in the functional recovery of severe brain-injured patients. In this thalamic pathway (see the mesocircuit model below), dopamine exerts effects on the thalamus and the basal ganglia, which then connects to the supplementary and primary motor areas, the dorsolateral prefrontal cortex, and the limbic structures [93].

Dopaminergic agents have thus been suggested to increase thalamic tonus firing via the striato-thalamic projections [94]. The *mesocircuit model* has been proposed to explain the various pharmacological effects on the recovery of consciousness [95] (Fig. 11.5). The central thalamic nuclei (CTN) seem particularly important in

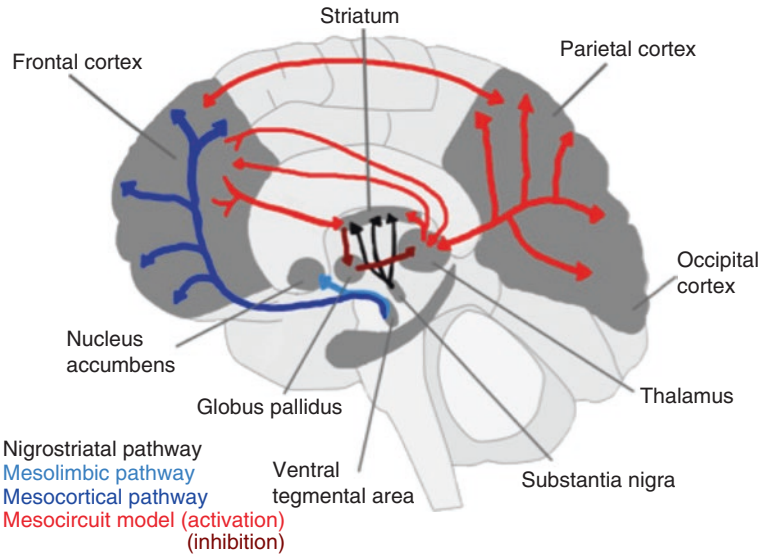

Fig. 11.4 Schematic illustration of the potential mechanisms of action of pharmacological agents on the level of consciousness. According to the mesocircuit model [74], dopamine facilitation of the striatum's output or the direct modulation of the frontal cortex would explain the restoration of anterior forebrain activity within the loop connections of the frontal cortex, striatum, pallidum, and thalamus. Zolpidem would act more on the globus pallidus by directly inhibiting it (Taken from [92])

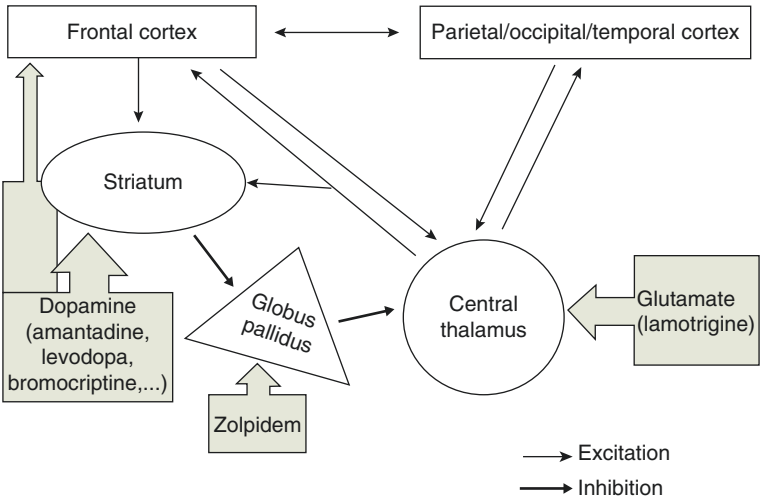

Fig. 11.5 The mesocircuit model that aims to explain the mechanisms of pharmacologically induced recovery of consciousness (Adapted from [74])

the emergence of consciousness. They receive ascending projections coming from the brainstem encompassing the arousal systems that control the activity of many cortical and thalamic neurons during the sleep-wake cycle. The CTN are strongly nerved by cholinergic, serotoninergic, noradrenergic afferents of the arousal system in the brainstem. These same neurons of the CTN are also innervated by the downward projections coming from the areas of the frontoparietal cortex. Collectively, these ascending and descending pathways seem to modulate the level of consciousness [95]. The frontoparietal cortex (and its subcortical modulation via striatum, globus pallidus, and thalamus) is also prevalent for the emergence of consciousness. Thalamocortical projections coming from the CTN activate in normal conditions the neurons of the cortex and striatum. Lesions at this level result in a reduction of cerebral metabolism. Neurons of the striatum inhibit the internal globus pallidus but require a strong basic synaptic activity and elevated levels of dopaminergic innervations in order to maintain their state in activity. Without projections of the striatum to the globus pallidus (e.g., by a lack of dopaminergic innervations), the globus pallidus itself will inhibit the CTN, which in turn will inhibit the cortical structures, and this sequence could, thus, generate consciousness disorders. Disturbances in this mesocircuit influence the total dynamics of the dominating corticothalamic and frontoparietal systems [74]. Dopaminergic drugs could, therefore, facilitate projections of the striatum on the globus pallidus, which would modulate the frontoparietal cortical neurons and would restore the cortico-subcortical loops. Zolpidem is thought to act directly on the globus pallidus and would make it possible to inhibit it (as it is usually the case due to the action of the striatum), which would also restore the activity of the CTN, whereas the glutamatergic agents (e.g., lamotrigine) would intervene directly on the CTN (Fig. 11.5).

Single-Subject Methods to Assess the Off-Label Use of Specific Medication

As noted, there are very few drugs for which we have strong evidence of clinical efficacy in treating specific cognitive or behavioral problems after severe TBI. Important questions remain even for the most rigorously studied drugs about the most likely responders and the optimal treatment timing, dosage, and duration. For most of the drugs in this review, we have even less evidence: evidence from other populations coupled with anecdotal evidence or evidence from small or methodologically flawed studies. Nevertheless, many of these drugs are in prevalent use in an “off-label” fashion in the hope that they will be effective [96]. If the evidence does not allow us to predict a positive response with confidence before we initiate treatment, then surely we have a responsibility to know after treatment whether the drug resulted in clinical improvement and whether it produced important adverse effects. Thus, a practitioner using psychoactive drugs off-label should have a plan in place for determining the drug’s effects in retrospect and for determining when to consider tapering the drug in the future.

Single-subject experimental designs, also referred to as "N-of-1 studies," provide useful options for evaluating a drug's effect in the individual patient [97, 98]. In this approach, the tools of research are used to answer important clinical questions in the individual. The generalizability of this answer is not of concern as long as we know the effects in the patient we are treating. In the facility of one of the authors (JW), this process, within certain well-defined constraints, is not defined as research, does not require individual IRB review, and does not require informed consent to participate in research (though we are always careful to discuss the fact that the treatment itself is off-label). Single-subject designs may include randomization, specific schedules of drug administration, use of specific measurement tools, and sometimes blinded or placebo-controlled administration.

There are three basic designs that are most applicable to the evaluation of drug effects: A-B designs, A-B-A designs, and repeated crossover designs, in increasing order or rigor [99]. For all of these designs, the first task is to select the outcome measures that will be used to assess the drug's effects. Whenever possible, we select a measure of a very proximal outcome of the drug that may or may not be clinically meaningful, but that will help us ensure that the drug, at the dose given, is physiologically active. For example, in the hypothetical scenario where we hope to increase arousal to achieve more reliable command following, we might choose a measure of amount of time spent with the eyes open as a measure of the arousal response, though it is not our ultimate clinical goal. We also need, of course, a measure of the clinical goal; in this case, we might choose percent of a standard set of commands that are followed in each session. Finally, when we know that certain adverse effects of the drug are particularly likely, we might have in place a measure of those effects to alert us to their increase.

In planning the drug assessment, we must decide between standardized and psychometrically evaluated measures and measures tailored to the individual patient's problem. We rely on standardized measures where they are clearly applicable to the patient's problem, but often our treatment goals are too specific to match any existing measure, and then we must create one for the individual. This is typically a team-centered process and may be prompted by such questions as, "How would you know if this drug is having the desired effects? What would you actually observe if the drug does increase ___? How would you measure that change?"

In the A-B design, one begins collecting data with the chosen outcome measures for a period of time (the A phase) before the drug is started, conducting repeated measurements. Then one continues with those same repeated measurements after introducing the drug (the B phase), looking for a change in the measures that corresponds to the transition from A to B. In some cases visual inspection may reveal a clear change in the level of performance. Statistical evaluation is more controversial. In many cases the multiple performance data points are not statistically independent, violating the assumptions of many traditional statistical tests. One crude statistical approach involves a "celeration line" [100]. In this technique, a regression line is plotted through the A-phase data and continued forward into the B phase. The actual B-phase data points that lie above and below the celeration line are counted and subjected to a binomial test. If there is no drug effect, one would predict that

approximately 50% of B-phase data will likely be above and 50% below the line. Sharp deviation from this 50/50 ratio suggests a drug effect. However, it has been pointed out that, unless there is a very large volume of A-phase data and/or the variability in the A-phase is low, the confidence interval around the celeration line is likely to be wide. This means that having far more than 50% of B-phase data above or below all possible celeration lines could occur easily by chance (Fig. 11.6).

The A-B-A design is identical except that, after an interval of treatment, the drug is withdrawn again and one looks for a drop in performance that corresponds to the transition from B back to A (after which, of course, the drug can be reintroduced, if appropriate). In the repeated crossover design, one transitions back and forth between providing the drug and withholding the drug, ideally at random intervals, collecting the same outcome data throughout. In this design, the repeated crossovers reduce the likelihood that some other intervening events (an illness, another treatment, etc.) might actually be responsible for the change, since no other event is likely to follow the same randomly reversing schedule.

The A-B design is the most feasible to implement in the clinical setting, since it corresponds to routine clinical practice aside from the fact that measurement begins prior to treatment. Unfortunately, this design rarely provides a clear conclusion, as noted above. In addition to performance variability, if there is already a non-zero slope, one is challenged to determine that the slope is changed by the treatment. Just as in formal research, more variability requires a larger amount of data to reach conclusions, and this is often not feasible to collect in a time-limited clinical program. In addition, if the drug being administered requires gradual dose increases, this further undermines the ability to link behavioral changes to the drug.

The A-B-A design overcomes some, but not all, of these problems. Variability in the measured performance still presents a challenge, as does gradual introduction and withdrawal of the drug. However, the confounding between an ongoing recovery slope and the anticipated drug effect is addressed, because in the reversal from B back to A, recovery should still lead to improvement, whereas the drug withdrawal should lead to deterioration (Fig. 11.6). If the data clearly support the notion that the drug was associated with the improvement and deterioration, one can be reasonably confident of that conclusion. However, if improvement and deterioration linked to the drug are not evident, this could be due to excess variability, to the fact that ongoing recovery outweighs drug withdrawal effects, or to the fact that recovery has proceeded to the point that the drug is no longer needed. Although this is a scientific limitation of the A-B-A design, it is less of a limitation clinically. The main clinical question once a patient is receiving a drug is whether they should stop it or continue it.

The strongest design in terms of the ability to link any performance changes to the drug is the multiple crossover design. If a sufficient number of crossovers are performed at random intervals, then drug condition is unlikely to be confounded with time (recovery) or other medical or social events (Fig. 11.6). The main limitation of this design relates to the pharmacokinetics of the drug of interest. This design is well suited to drugs with rapid onsets of action which do not need to be introduced or withdrawn gradually, such as the psychostimulants [44]. Such drugs can be randomized at intervals of one to a few days, with little carryover of the drug's behavioral effects. For drugs with slower onsets of action (e.g., selective serotonin reuptake inhibitors) or those that require gradual drug titration (e.g., bromocriptine), such designs are rarely feasible.

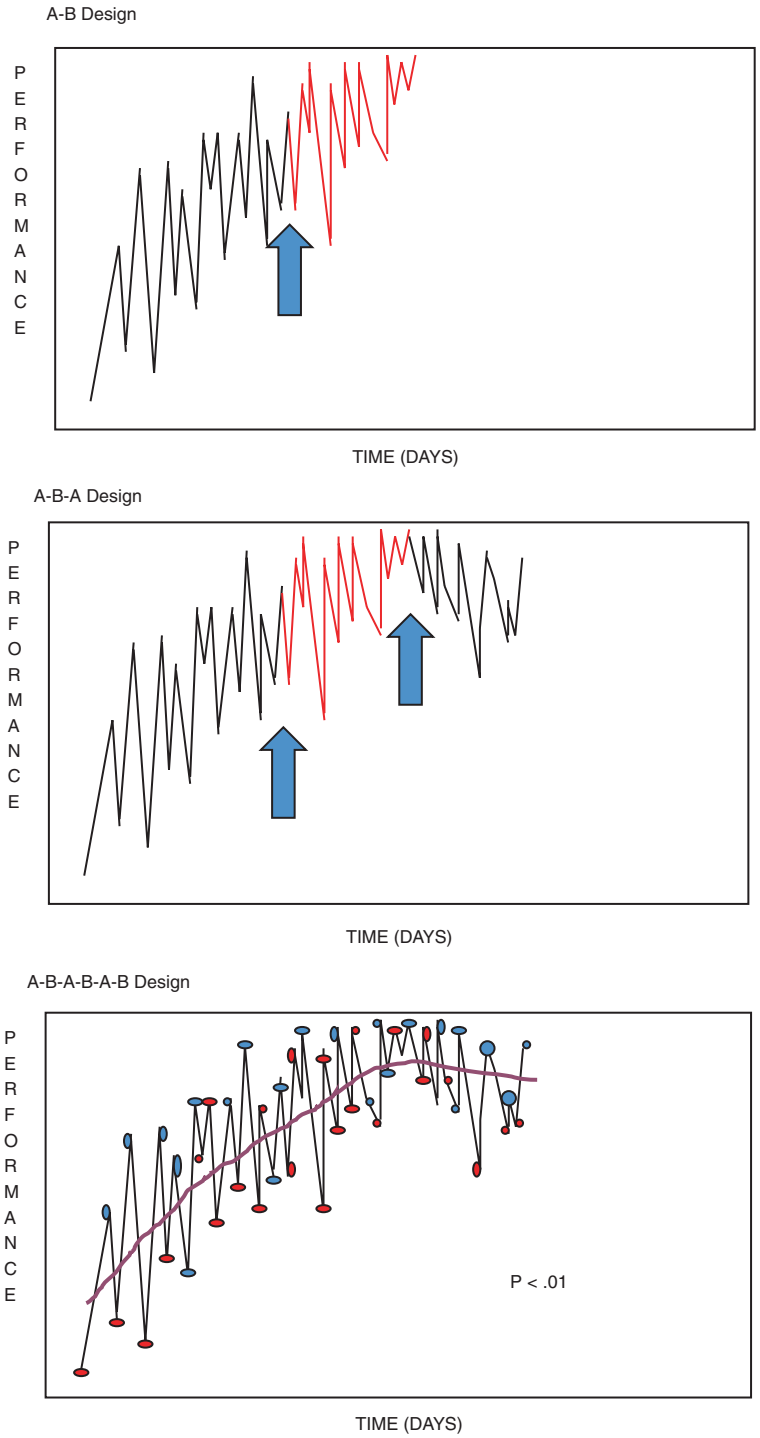

Fig. 11.6 Three basic designs used for the evaluation of drug effects

Weighing patient, drug, and measurement factors together suggests an optimal management approach [101]. In the early weeks and months post-injury, off-label prescribing of psychoactive drugs should be minimized. By definition, the effects of such drugs are not known with confidence and have a reasonable likelihood of impairing as well as facilitating recovery. Because of the natural slope and variability of recovery seen in this phase, it is highly unlikely that the effect of the drug chosen can be determined with confidence. Drugs that have been shown in large group studies to benefit most patients treated can be used in the early period, even though their effects may not be demonstrable in the individual. As recovery slows and variability in performance diminishes, the mandate to intervene to augment natural recovery becomes more pressing, and the ability of the measurement methods to document a treatment response becomes greater.

In practice, it remains useful to define patient-specific goals and measure performance with quantitative behavioral metrics before committing to pharmacologic intervention. The preliminary data may suggest that it will be impossible to evaluate a treatment response in the time available, that improvement over time is sufficiently brisk that there is no urgency to intervene, or that the pattern suggests another treatment approach rather than medication. But where the preliminary data demonstrates modest variability and lack of natural improvement, one can move forward with creative treatment evaluation methods.

Conclusion

Amantadine is the only drug with strong evidence from randomized controlled trials to demonstrate an impact on recovery of consciousness in DOC [24]. Even for amantadine, questions remain regarding its benefits for those with non-traumatic injuries, as well as the optimal dose, timing, and duration of treatment. Zolpidem has clearly been shown to lead to abrupt increases in the level of consciousness in a small minority of DOC patients, but, as yet, the factors that predict drug response are not fully known.

No strong evidence currently supports or disproves the use of other pharmacological agents in order to improve the level of consciousness in DOC patients. As discussed, a number of small and uncontrolled case or cohort studies have reported a positive clinical response. Transitory or permanent improvements have been observed among some UWS or MCS patients of various etiologies. Reported effects were variable, ranging from increase in wakefulness, partial recovery of consciousness, and motor, verbal, or communication functions to full recovery of cognitive functioning.

Some of the reviewed treatments (e.g., amantadine, zolpidem, baclofen) seem to benefit patients with severe DOC, whereas others (e.g., methylphenidate, lamotrigine) seem to possibly be more beneficial for brain-damaged but conscious patients improving their attention-deficit disorder. Positive drug effects have been observed from a single dose (e.g., zolpidem) or from continuous treatment (e.g., amantadine, baclofen, levodopa).

These studies mainly come from case or cohort reports which cannot disentangle the drug effect from natural recovery. Studies are also influenced by the extreme

heterogeneity of DOC, such as the site of neuropathological lesions, time elapsed between injury and the introduction of the treatment, confounding drugs received, and medical comorbidities. Moreover, it is difficult to compare between studies since they lack homogeneity in methodology and differ in the duration of treatment, administered doses, and patients' demographics and clinical status. Measurement tools and behavioral scales are also very different across studies, and a standardization of bedside assessment seems necessary. Additional placebo-controlled, double-blind randomized multicenter studies are necessary before drawing conclusions about the role of other medications in these challenging patients.

Importantly, there is little reason to believe that any pharmacologic agent can benefit all patients with DOC, given the heterogeneity of pharmacologic mechanisms and the variation in site and severity of neuropathology. Thus, research is needed to understand the pharmacologic targets relevant to restoration of consciousness and to identify biomarkers that allow selection of patient subgroups with the ability to respond to specific pharmacologic probes. This will allow conduct of randomized trials in patient groups "enriched" with the necessary brain substrates for therapeutic response. Efforts to advance pharmacologic treatments for DOC should focus on the conduct of large parallel group studies. Clinicians practicing in the face of minimal evidence should consider deferring off-label drug intervention to the point in recovery when positive or negative impacts of the drug can be recognized.

References

1. Plum F, Posner JB. The diagnosis of stupor and coma. Philadelphia: F. A. Davis; 1983.
2. The Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state (1). N Engl J Med. 1994;330(21):1499–508.
3. Laureys S, Celesia GG, Cohadon F, Lavrijsen J, Leon-Carrion J, Sannita WG, Sazbon L, Schmutzhard E, von Wild KR, Zeman A, Dolce G. Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. BMC Med. 2010;8:68.
4. Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, Kelly JP, Rosenberg JH, Whyte J, Zafonte RD, Zasler ND. The minimally conscious state: definition and diagnostic criteria. Neurology. 2002;58(3):349–53.
5. Ciurleo R, Bramanti P, Calabro RS. Pharmacotherapy for disorders of consciousness: are 'awakening' drugs really a possibility? Drugs. 2013;73(17):1849–62.
6. Abbate C, Trimarchi PD, Basile I, Mazzucchi A, Devalle G. Sensory stimulation for patients with disorders of consciousness: from stimulation to rehabilitation. Front Hum Neurosci. 2014;8:616.
7. Klingshirn H, Grill E, Bender A, Strobl R, Mittrach R, Braitmayer K, Muller M. Quality of evidence of rehabilitation interventions in long-term care for people with severe disorders of consciousness after brain injury: a systematic review. J Rehabil Med. 2015;47(7):577–85.
8. Magrassi L, Maggioni G, Pistarini C, Di Perri C, Bastianello S, Zippo AG, Iotti GA, Biella GE, Imberti R. Results of a prospective study (CATS) on the effects of thalamic stimulation in minimally conscious and vegetative state patients. J Neurosurg. 2016;125(4):972–81.
9. Chew E, Zafonte R. Pharmacological management of neurobehavioral disorders following traumatic brain injury—a state-of-the-art review. J Rehabil Res Dev. 2009;46(6):851–79.
10. Robbins T. Arousal systems and attentional processes. Biol Psychol. 1997;45(1–3):57–71.
11. Harris CD. Neurophysiology of sleep and wakefulness. Respir Care Clin N Am. 2005;11(4):567–86.

12. Zafonte R, Lexell J, Cullen N. Possible applications for dopaminergic agents following traumatic brain injury: part 2. J Head Trauma Rehabil. 2001;16(1):112–6.
13. Saniova B, Drobny M, Kneslova L, Minarik M. The outcome of patients with severe head injuries treated with amantadine sulphate. J Neural Transm. 2004;111(4):511–4.
14. Whyte J, Katz D, Long D, DiPasquale MC, Polansky M, Kalmar K, Giacino J, Childs N, Mercer W, Novak P, Maurer P, Eifert B. Predictors of outcome in prolonged posttraumatic disorders of consciousness and assessment of medication effects: a multicenter study. Arch Phys Med Rehabil. 2005;86(3):453–62.
15. Sawyer E, Mauro L, Ohlinger M. Amantadine enhancement of arousal and cognition after traumatic brain injury. Ann Pharmacother. 2008;42(2):247–52.
16. Born JD. The Glasgow-Liège Scale. Prognostic value and evaluation of motor response and brain stem reflexes after severe head injury. Acta Neurochir. 1988;95:49–52.
17. Folstein M, Robins L, Helzer J. The mini-mental state examination. Arch Gen Psychiatry. 1983;40(7):812.
18. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet. 1975; 1(7905):480–4.
19. Rappaport M, Hall KM, Hopkins K, Belleza T, Cope DN. Disability rating scale for severe head trauma: coma to community. Arch Phys Med Rehabil. 1982;63(3):118–23.
20. Meythaler JM, Brunner RC, Johnson A, Novack TA. Amantadine to improve neurorecovery in traumatic brain injury-associated diffuse axonal injury: a pilot double-blind randomized trial. J Head Trauma Rehabil. 2002;17(4):300–13.
21. Rappaport M. The Coma/Near Coma Scale. 2000. http://www.tbims.org/combi/cnc
22. Zafonte R, Watanabe T, Mann N. Amantadine: a potential treatment for the minimally conscious state. Brain Inj. 1998;12(7):617–21.
23. Avecillas-Chasin JM, Barcia JA. Effect of amantadine in minimally conscious state of non-traumatic etiology. Acta Neurochir. 2014;156(7):1375–7.
24. Giacino JT, Whyte J, Bagiella E, Kalmar K, Childs N, Khademi A, Eifert B, Long D, Katz DI, Cho S, Yablon SA, Luther M, Hammond FM, Nordenbo A, Novak P, Mercer W, Maurer-Karattup P, Sherer M. Placebo-controlled trial of amantadine for severe traumatic brain injury. N Engl J Med. 2012;366(9):819–26.
25. Reynolds JC, Rittenberger JC, Callaway CW. Methylphenidate and amantadine to stimulate reawakening in comatose patients resuscitated from cardiac arrest. Resuscitation. 2013;84(6): 818–24.
26. Horiguchi J, Inami Y, Shoda T. Effects of long-term amantadine treatment on clinical symptoms and EEG of a patient in a vegetative state. Clin Neuropharmacol. 1990;13(1):84–8.
27. Estraneo A, Pascarella A, Moretta P, Loreto V, Trojano L. Clinical and electroencephalographic on-off effect of amantadine in chronic non-traumatic minimally conscious state. J Neurol. 2015;262(6):1584–6.
28. Schnakers C, Hustinx R, Vandewalle G, Majerus S, Moonen G, Boly M, Vanhaudenhuyse A, Laureys S. Measuring the effect of amantadine in chronic anoxic minimally conscious state. J Neurol Neurosurg Psychiatry. 2008;79(2):225–7.
29. Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil. 2004;85(12):2020–9.
30. Stelmaschuk S, Will MC, Meyers T. Amantadine to treat cognitive dysfunction in moderate to severe traumatic brain injury. J Trauma Nurs. 2015;22(4): 194–203; quiz E191–2.
31. Haig A, Ruess J. Recovery from vegetative state of six months' duration associated with Sinemet (levodopa/carbidopa). Arch Phys Med Rehabil. 1990;71(13):1081–3.
32. Matsuda W, Matsumura A, Komatsu Y, Yanaka K, Nose T. Awakenings from persistent vegetative state: report of three cases with parkinsonism and brain stem lesions on MRI. J Neurol Neurosurg Psychiatry. 2003;74(11):1571–3.
33. Matsuda W, Komatsu Y, Yanaka K, Matsumura A. Levodopa treatment for patients in persistent vegetative or minimally conscious states. Neuropsychol Rehabil. 2005;15(3–4):414–27.
34. Krimchansky B, Keren O, Sazbon L, Groswasser Z. Differential time and related appearance of signs, indicating improvement in the state of consciousness in vegetative state traumatic brain injury (VS-TBI) patients after initiation of dopamine treatment. Brain Inj. 2004;18(11): 1099–105.

35. Ugoya SO, Akinyemi RO. The place of L-dopa/carbidopa in persistent vegetative state. Clin Neuropharmacol. 2010;33(6):279–84.
36. Passler MA, Riggs RV. Positive outcomes in traumatic brain injury-vegetative state: patients treated with bromocriptine. Arch Phys Med Rehabil. 2001;82(3):311–5.
37. Whyte J, Vaccaro M, Grieb-Neff P, Hart T, Polansky M, Coslett HB. The effects of bromocriptine on attention deficits after traumatic brain injury: a placebo-controlled pilot study. Am J Phys Med Rehabil. 2008;87(2):85–99.
38. Millan M, Maiofiss L, Cussac D, Audinot V, Boutin J, Newman-Tancredi A. Differential actions of antiparkinson agents at multiple classes of monoaminergic receptor. I. A multivariate analysis of the binding profiles of 14 drugs at 21 native and cloned human receptor subtypes. J Pharmacol Exp Ther. 2002;303(2):791–804.
39. Fridman E, Calvar J, Bonetto M, Gamzu E, Krimchansky B, Meli F, Leiguarda R, Zafonte R. Fast awakening from minimally conscious state with apomorphine. Brain Inj. 2009;23(2): 172–7.
40. Laureys S, Faymonville ME, Luxen A, Lamy M, Franck G, Maquet P. Restoration of thalamocortical connectivity after recovery from persistent vegetative state. Lancet. 2000; 355(9217):1790–1.
41. Fridman E, Krimchansky B, Bonetto M, Galperin T, Gamzu E, Leiguarda R, Zafonte R. Continuous subcutaneous apomorphine for severe disorders of consciousness after traumatic brain injury. Brain Inj. 2010;24(4):636–41.
42. Moein H, Khalili H, Keramatian K. Effect of methylphenidate on ICU and hospital length of stay in patients with severe and moderate traumatic brain injury. Clin Neurol Neurosurg. 2006;108(6):539–42.
43. Kim YW, Shin JC, An YS. Effects of methylphenidate on cerebral glucose metabolism in patients with impaired consciousness after acquired brain injury. Clin Neuropharmacol. 2009;32(6):335–9.
44. Martin R, Whyte J. The effects of methylphenidate on command following and yes/no communication in persons with severe disorders of consciousness: a meta-analysis of n-of-1 studies. Am J Phys Med Rehabil. 2007;86(8):613–20.
45. Kaelin D, Cifu D, Mathies B. Methylphenidate effect on attention deficit in the acutely brain-injured adult. Arch Phys Med Rehabil. 1996;77(1):6–9.
46. Plenger P, Dixon C, Castillo R, Frankowski R, Yablon S, Levin H. Subacute methylphenidate treatment for moderate to moderately severe traumatic brain injury: a preliminary double-blind placebo-controlled study. Arch Phys Med Rehabil. 1996;77(6):536–40.
47. Whyte J, Hart T, Schuster K, Fleming M, Polansky M, Coslett H. Effects of methylphenidate on attentional function after traumatic brain injury. A randomized, placebo-controlled trial. Am J Phys Med Rehabil. 1997;76(6):440–50.
48. Whyte J, Hart T, Vaccaro M, Grieb-Neff P, Risser A, Polansky M, Coslett H. Effects of methylphenidate on attention deficits after traumatic brain injury: a multidimensional, randomized, controlled trial. Am J Phys Med Rehabil. 2004;83(6):401–20.
49. Kim J, Whyte J, Patel S, Europa E, Wang J, Coslett HB, Detre JA. Methylphenidate modulates sustained attention and cortical activation in survivors of traumatic brain injury: a perfusion fMRI study. Psychopharmacology (Berl). 2012;222(1):47–57.
50. Patrick P, Buck M, Conaway M, Blackman J. The use of dopamine enhancing medications with children in low response states following brain injury. Brain Inj. 2003;17(6):497–506.
51. Clauss RP, Guldenpfennig WM, Nel HW, Sathekge MM, Venkannagari RR. Extraordinary arousal from semi-comatose state on zolpidem. A case report. S Afr Med J. 2000;90(1): 68–72.
52. Clauss RP, Nel W. Drug induced arousal from the permanent vegetative state. NeuroRehabilitation. 2006;21(1):23–8.
53. Hagen C, Malkmus D, Durham P. Levels of cognitive functioning. Downey: Rancho Los Amigos Hospital Inc.; 1987.
54. Brefel-Courbon C, Payoux P, Ory F, Sommet A, Slaoui T, Raboyeau G, Lemesle B, Puel M, Montastruc JL, Demonet JF, Cardebat D. Clinical and imaging evidence of zolpidem effect in hypoxic encephalopathy. Ann Neurol. 2007;62(1):102–5.

55. Cohen SI, Duong TT. Increased arousal in a patient with anoxic brain injury after administration of zolpidem. Am J Phys Med Rehabil. 2008;87(3):229–31.
56. Shames JL, Ring H. Transient reversal of anoxic brain injury-related minimally conscious state after zolpidem administration: a case report. Arch Phys Med Rehabil. 2008;89(2):386–8.
57. Appu M, Noetzel M. Clinically significant response to zolpidem in disorders of consciousness secondary to anti-N-methyl-D-aspartate receptor encephalitis in a teenager: a case report. Pediatr Neurol. 2014;50(3):262–4.
58. Lo Y, Tan E, Ratnagopal P, Chan L, Tan T. Zolpidem and its effects on hypoxic encephalopathy. Ann Neurol. 2008;64(4):477–8.
59. Singh R, McDonald C, Dawson K, Lewis S, Pringle A, Smith S, Pendland B. Zolpidem in a minimally conscious state. Brain Inj. 2008;22(1):103–6.
60. Whyte J, Myers R. Incidence of clinically significant responses to zolpidem among patients with disorders of consciousness: a preliminary placebo controlled trial. Am J Phys Med Rehabil. 2009;88(5):410–8.
61. Whyte J, Rajan R, Rosenbaum A, Katz D, Kalmar K, Seel R, Greenwald B, Zafonte R, Demarest D, Brunner R, Kaelin D. Zolpidem and restoration of consciousness. Am J Phys Med Rehabil. 2014;93(2):101–13.
62. Machado C, Estévez M, Pérez-Nellar J, Gutiérrez J, Rodríguez R, Carballo M, Chinchilla M, Machado A, Portela L, García-Roca MC, Beltrán C. Autonomic, EEG, and behavioral arousal signs in a PVS case after zolpidem intake. Can J Neurol Sci. 2011;38(2):341–4.
63. Machado C, Estevez M, Rodriguez R, Perez-Nellar J, Chinchilla M, DeFina P, Leisman G, Carrick FR, Melillo R, Schiavi A, Gutierrez J, Carballo M, Machado A, Olivares A, Perez-Cruz N. Zolpidem arousing effect in persistent vegetative state patients: autonomic, EEG and behavioral assessment. Curr Pharm Des. 2014;20(26):4185–202.
64. Thonnard M, Gosseries O, Demertzi A, Lugo Z, Vanhaudenhuyse A, Bruno M, Chatelle C, Thibaut T, Charland-Verville V, Habbal D, Schnakers C, Laureys S. Effect of zolpidem in chronic disorders of consciousness: a prospective open label study. Funct Neurol. 2013;28(4):259–64.
65. Du B, Shan A, Zhang Y, Zhong X, Chen D, Cai K. Zolpidem arouses patients in vegetative state after brain injury: quantitative evaluation and indications. Am J Med Sci. 2014;347(3):178–82.
66. Cohen L, Chaaban B, Habert MO. Transient improvement of aphasia with zolpidem. N Engl J Med. 2004;350(9):949–50.
67. Rodriguez-Rojas R, Machado C, Alvarez L, Carballo M, Estevez M, Perez-Nellar J, Pavon N, Chinchilla M, Carrick FR, DeFina P. Zolpidem induces paradoxical metabolic and vascular changes in a patient with PVS. Brain Inj. 2013;27(11):1320–9.
68. Chatelle C, Thibaut A, Gosseries O, Bruno MA, Demertzi A, Bernard C, Hustinx R, Tshibanda L, Bahri MA, Laureys S. Changes in cerebral metabolism in patients with a minimally conscious state responding to zolpidem. Front Hum Neurosci. 2014;8:917.
69. Williams ST, Conte MM, Goldfine AM, Noirhomme Q, Gosseries O, Thonnard M, Beattie B, Hersh J, Katz DI, Victor JD, Laureys S, Schiff ND. Common resting brain dynamics indicate a possible mechanism underlying zolpidem response in severe brain injury. Elife. 2013;2:e01157.
70. Calabro RS, Arico I, De Salvo S, Conti-Nibali V, Bramanti P. Transient awakening from vegetative state: is high-dose zolpidem more effective? Psychiatry Clin Neurosci. 2015;69(2):122–3.
71. Clauss RP, Nel WH. Effect of zolpidem on brain injury and diaschisis as detected by 99mTc HMPAO brain SPECT in humans. Arzneimittelforschung. 2004;54(10):641–6.
72. Hall S, Yamawaki N, Fisher A, Clauss R, Woodhall G, Stanford I. GABA(A) alpha-1 subunit mediated desynchronization of elevated low frequency oscillations alleviates specific dysfunction in stroke—a case report. Clin Neurophysiol. 2010;121(4):549–55.
73. Pistoia F, Sara M, Sacco S, Franceschini M, Carolei A. Silencing the brain may be better than stimulating it. The GABA effect. Curr Pharm Des. 2014;20(26):4154–66.
74. Schiff ND. Recovery of consciousness after brain injury: a mesocircuit hypothesis. Trends Neurosci. 2010;33(1):1–9.

75. Pistoia F, Sacco S, Sara M, Franceschini M, Carolei A. Intrathecal baclofen: effects on spasticity, pain, and consciousness in disorders of consciousness and locked-in syndrome. Curr Pain Headache Rep. 2015;19(1):466.
76. Turner M. Early use of intrathecal baclofen in brain injury in pediatric patients. Acta Neurochir. 2003;87:81–3.
77. Kawecki Z, Kwiatkowski S, Grzegorzewski P, Szlachta Jezioro I. Sudden improvement of all neurological functions after general anesthesia and two-day intrathecal infusion of baclofen in a child with primary brain-stem injury. Przegl Lek. 2007;64(2):13–4.
78. Sarà M, Sacco S, Cipolla F, Onorati P, Scoppetta C, Albertini G, Carolei A. An unexpected recovery from permanent vegetative state. Brain Inj. 2007;21(1):101–3.
79. Taira T, Hori T. Intrathecal baclofen in the treatment of post-stroke central pain, dystonia, and persistent vegetative state. Acta Neurochir Suppl. 2007;97(Pt 1):227–9.
80. Sarà M, Pistoia F, Mura E, Onorati P, Govoni S. Intrathecal baclofen in patients with persistent vegetative state: 2 hypotheses. Arch Phys Med Rehabil. 2009;90(7):1245–9.
81. Al-Khodairy AT, Wicky G, Nicolo D, Vuadens P. Influence of intrathecal baclofen on the level of consciousness and mental functions after extremely severe traumatic brain injury: brief report. Brain Inj. 2015;29(4):527–32.
82. Margetis K, Korfias SI, Gatzonis S, Boutos N, Stranjalis G, Boviatsis E, Sakas DE. Intrathecal baclofen associated with improvement of consciousness disorders in spasticity patients. Neuromodulation. 2014;17(7):699–704.
83. Hoarau X, Richer E, Dehail P, Cuny E. Comparison of long-term outcomes of patients with severe traumatic or hypoxic brain injuries treated with intrathecal baclofen therapy for dysautonomia. Brain Inj. 2012;26(12):1451–63.
84. Hoarau X, Richer E, Dehail P, Cuny E. A 10-year follow-up study of patients with severe traumatic brain injury and dysautonomia treated with intrathecal baclofen therapy. Brain Inj. 2012;26(7–8):927–40.
85. Taira T. Intrathecal administration of GABA agonists in the vegetative state. Prog Brain Res. 2009;177:317–28.
86. Coulter D. Antiepileptic drug cellular mechanisms of action: where does lamotrigine fit in? J Child Neurol. 1997;12(1):2–9.
87. Calabresi P, Centonze D, Cupini L, Costa C, Pisani F, Bernardi G. Ionotropic glutamate receptors: still a target for neuroprotection in brain ischemia? Insights from in vitro studies. Neurobiol Dis. 2003;12:82–8.
88. Showalter P, Kimmel D. Stimulating consciousness and cognition following severe brain injury: a new potential clinical use for lamotrigine. Brain Inj. 2000;14:997–1001.
89. Pistoia F, Mura E, Govoni S, Fini M, Sarà M. Awakenings and awareness recovery in disorders of consciousness: is there a role for drugs? CNS Drugs. 2010;24(8):625–38.
90. Clauss RP. Neurotransmitters in coma, vegetative and minimally conscious states, pharmacological interventions. Med Hypotheses. 2010;75(3):287–90.
91. Stahl S. Essential psychopharmacology: neuroscientific basis and practical applications. New York: Press CU; 2000.
92. Gosseries O, Charland-Verville V, Thonnard M, Bodart O, Laureys S, Demertzi A. Amantadine, apomorphine and zolpidem in the treatment of disorders of consciousness. Curr Pharm Des. 2014;20(26):4167–84.
93. Oliveira L, Fregni F. Pharmacological and electrical stimulation in chronic disorders of consciousness: new insights and future directions. Brain Inj. 2011;25(4):315–27.
94. Schiff ND. Central thalamic deep-brain stimulation in the severely injured brain: rationale and proposed mechanisms of action. Ann N Y Acad Sci. 2009;1157:101–16.
95. Schiff ND. Recovery of consciousness after severe brain injury: the role of arousal regulation mechanisms and some speculation on the heart-brain interface. Cleve Clin J Med. 2010;77(Suppl 3):S27–33.
96. Hammond FM, Barrett RS, Shea T, Seel RT, McAlister TW, Kaelin D, Ryser DK, Corrigan JD, Cullen N, Horn SD. Psychotropic medication use during inpatient rehabilitation for traumatic brain injury. Arch Phys Med Rehabil. 2015;96(8 Suppl):S256–3. e214

97. Larson EB. N-of-1 trials: a new future? J Gen Intern Med. 2010;25(9):891–2.
98. Lillie EO, Patay B, Diamant J, Issell B, Topol EJ, Schork NJ. The n-of-1 clinical trial: the ultimate strategy for individualizing medicine? Pers Med. 2011;8(2):161–73.
99. Backman CL, Harris SR, Chisholm JA, Monette AD. Single-subject research in rehabilitation: a review of studies using AB, withdrawal, multiple baseline, and alternating treatments designs. Arch Phys Med Rehabil. 1997;78(10):1145–53.
100. Ottenbacher KJ. Evaluating clinical change. Baltimore: Williams and Wilkins; 1986.
101. Whyte J. Design of brain injury rehabilitation treatment research. Handb Clin Neurol. 2015;128:779–94.

Chapter 12
New Therapeutic Options for the Treatment of Patients with Disorders of Consciousness: The Field of Neuromodulation

Aurore Thibaut and Nicholas D. Schiff

Abstract Neuromodulation techniques aimed at normalizing the neurophysiologic disturbance produced by brain lesions or dysfunction have been studied for years in attempts to modulate brain activity to treat several neurological diseases. The field of (non)invasive brain stimulation offers a valuable alternative to improve the recovery of severely brain-injured patients with disorders of consciousness, a population that lacks of effective treatment options, especially at the chronic stage. We here describe invasive and noninvasive brain stimulation techniques, namely, deep brain stimulation (DBS) and transcranial direct current stimulation (tDCS), as therapeutic options for patients with DOC. DBS has shown to induce extensive behavioral improvement after the implantation of an electrical stimulator in the intralaminar nuclei in case reports. However, large controlled clinical trials have to be conducted in order to confirm the clinical benefit of this treatment. Regarding tDCS, the first studies, targeting the left prefrontal cortex, have shown encouraging results, with significant behavioral improvements, in both acute and chronic patients. Besides behavioral improvements, mechanisms underlying the effects of these neuromodulation techniques need to be further investigated. The mesocircuit model, by integrating the fronto-striato-thalamic loop, provides a conceptual foundation to explain the effects of several treatments having shown some effectiveness in the recovery of patients with DOC.

A. Thibaut, Ph.D. (✉)
Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium

Neuromodulation Center, Spaulding Rehabilitation Hospital, Harvard Medical School, 79/96 13th street, 02129 Boston, MA, USA
e-mail: athibaut@ulg.ac.be

N.D. Schiff, M.D.
Feil Family Brain and Mind Research Institute, Weill Cornell Medical College, New York, NY, USA

C. Schnakers, S. Laureys (eds.), *Coma and Disorders of Consciousness*,
DOI 10.1007/978-3-319-55964-3_12

Introduction

While significant progress has been made in understanding the neural correlates of disorders of consciousness (DOC), treatment options for patients with altered states of consciousness available today remain very limited. Moreover, when these treatments are effective, the underlying mechanisms are still almost unknown. Recent discoveries demonstrating the inherent plasticity of the brain suggest a wide range of therapeutic possibilities. Indeed, in the past 10 years, a number of studies have reported that some patients in MCS could spontaneously improve even several years after the insult [1–3]. Studies of treatments improving cognitive abilities in patients with DOC have also shown that deep brain stimulation (DBS) of the intralaminar nuclei of the thalamus [4] and some pharmacological agents such as amantadine [5, 6], apomorphine [7], intrathecal baclofen [8], and zolpidem [9, 10] can improve behavioral signs of consciousness in some patients with DOC. However, so far, only amantadine has been shown to increase signs of consciousness in a large cohort of acute and subacute patients with DOC in a placebo-controlled trial [6]. In addition, the specific mechanisms underlying the recovery of behavioral signs of consciousness observed in such patients with DOC following the administration of these drugs are still poorly understood. We hence clearly need to improve our treatment options for the small—albeit existing—minority of patients who show clinically meaningful recovery of quality of life after chronic DOC [11]. Our next challenge is to better understand the mechanisms of action of these treatments when clinical improvement of patients is observed and how to possibly improve therapeutic options.

In this chapter, we describe the use of invasive and noninvasive brain stimulation (i.e., deep brain stimulation (DBS) and transcranial direct current stimulation (tDCS)) to improve the recovery of patients with DOC, as well as the current models that could explain the underlying neurophysiological mechanisms of these two neuromodulation techniques.

What Network to Stimulate

Frontoparietal Network

Studies of regional brain metabolism have sought to identify areas specifically involved in loss of consciousness, comparing brain metabolism of patients in vegetative state/unresponsive wakefulness syndrome (VS/UWS) and in minimally conscious state (MCS) with healthy controls. The results of these studies highlight the correlation of a widespread impairment of the frontoparietal network, encompassing midline (i.e., anterior cingulate cortex (ACC)/mesiofrontal and posterior cingulate cortex (PCC)/precuneus, related to internal awareness or self-related processes) and lateral (i.e., prefrontal and posterior parietal, related to awareness of the

environment) associative cortices, with a decreased level of consciousness [12–18]. The connectivity within the midline frontoparietal cortex, also called the default mode network (DMN), has been shown to reflect the level of consciousness of DOC patients [19]. Indeed, the connectivity of this network is correlated to the level of consciousness, ranging from patients in UWS/VS (low connectivity) to patients in MCS and to healthy controls (higher connectivity). In a more recent study, it has been observed that patients in UWS/VS have metabolic dysfunction in both thalami and both extrinsic/lateral and intrinsic/medial networks, also called the DMN (i.e., anterior cingulate/medial prefrontal cortex and posterior cingulate/precuneus), as compared to controls, while MCS patients showed metabolic dysfunction in both thalami but only in the intrinsic/medial network [20]. These studies point to the importance of both internal and external consciousness network in the recovery of consciousness.

Part of the external consciousness network, the dorsolateral prefrontal cortex (DLPFC) is a critical area for higher cognitive functions. This cortical region is connected to many brain areas such as the orbitofrontal cortex, the basal ganglia, the thalamus, and the associative cortical areas. It is thought to play an important integrating role in the motor and behavioral functions, as well as in the executive functions, such as planning, working memory, inhibition, and cognitive flexibility. Indeed, the DLPFC receives multisensory information from the parietal associative cortices and projects directly to subcortical monoaminergic and cholinergic neuronal populations within the brainstem [21–23]. Besides executive functions, the additional cortical and subcortical circuits with which the DLPFC is connected are more generally required for all complex mental activity. Indeed, the DLPFC is part of the functional executive control network, known to be related to external awareness [24]. Through these complex connections with cortical and subcortical brain areas, the DFPLC is a critical brain region for cognitive functions and integrations. It is part of the external consciousness network, as well as related to the recovery of consciousness [20]. Recent neuroimaging studies have shown the implication of the DFPLC in the efficacy of several treatments (e.g., zolpidem, amantadine, or noninvasive brain stimulation) aiming to improve signs of consciousness in DOC patients [5, 25, 26], further strengthening the importance of this region in recovery of consciousness (see below).

It is now widely admitted that the precuneus is another critical hub for consciousness recovery [13, 18, 27, 28]. Indeed, several studies have shown that, at rest, the precuneus is the most active area in healthy subjects, while it is the most impaired in patients in VS/UWS [29]. In addition, the recovery from VS/UWS seems to be paralleled by a recovery in brain metabolism in this region [12, 30]. Moreover, the precuneus is a critical hub of the DMN, which is also highly correlated with the level of consciousness [19, 27, 31, 32]. A recent functional magnetic resonance imaging (fMRI) study using tractography has anatomically objectified that patients with DOC demonstrate damages in fiber tracts connecting the precuneus with both cortical (i.e., temporoparietal junction and frontal medial cortex) and subcortical (i.e., thalamus and striatum) areas [33].

Mesocircuit Frontoparietal Model

In addition to the very strong evidence that activity within the frontoparietal network grades with level of recovery of consciousness, the key role of the anterior forebrain mesocircuit has been identified in recovery of consciousness after severe brain injuries [34]. These networks have critical functional and anatomical relationships that support a joint mesocircuit frontoparietal model [35] as reviewed below (Fig. 12.1).

The mesocircuit hypothesis emphasizes that the anterior forebrain is particularly vulnerable to downregulation due to widespread cerebral deafferentation that typically occurs following multifocal brain injuries [34]. The anterior forebrain mesocircuit itself prominently includes the frontal/prefrontal cortices and the striatopallidal modulatory system that regulates thalamic outflow back to the cortex and striatum. Neurons within the central thalamus have a crucial role in the mesocircuit based on their extensive anatomical connectivity with the forebrain [37], as

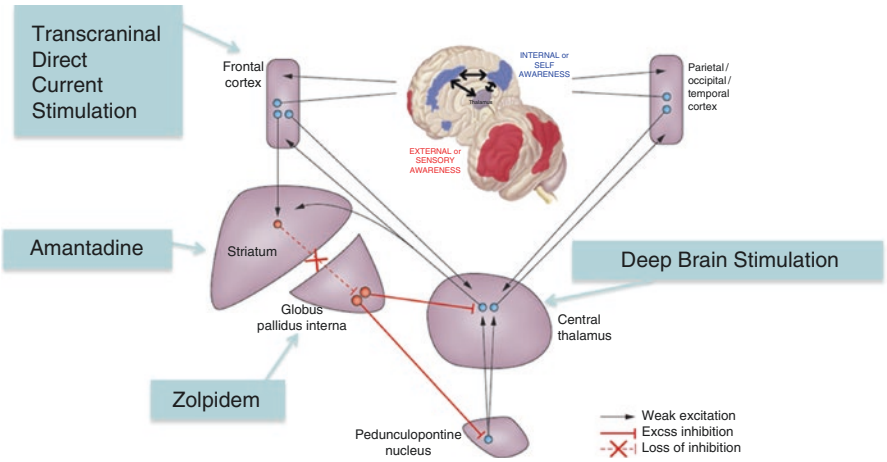

Fig. 12.1 The mesocircuit frontoparietal model. Reduction of thalamocortical and thalamostriatal outflow following deafferentation and loss of neurons from the central thalamus withdraws important afferent drive to the medium spiny neurons of the striatum, which may then fail to reach firing threshold because of their requirement for high levels of synaptic background activity. Loss of active inhibition from the striatum allows neurons of the globus pallidus interna (GPi) to tonically fire and provide active inhibition to their synaptic targets, including relay neurons of the already strongly disfacilitated central thalamus, and possibly also the projection neurons of the pedunculopontine nucleus. Several treatments that have shown promising results in the recovery of signs of consciousness in severely brain-injured patients are related to the mesocircuit model. A partial preservation of the prefrontal cortex (i.e., stimulated area) seems to be necessary to induce a clinical tDCS response [25]. The clinical improvement of a patient who responded to amantadine was correlated with an increase in brain metabolism with the frontoparietal network [5]. Zolpidem may reduce the inhibition of the thalamus by activating the striatum [34]. Finally, deep brain stimulation directly acts over the central thalamus aiming to stimulate the thalamocortical connectivity [4] (Adapted from [36])

well as their functional role in forebrain arousal regulation [38, 39]. Consistent with their unique geometry, pathological studies have shown strong correlation of the loss of these central thalamic neurons with the severity of structural brain injuries and level of functional outcomes ranging from disorders of consciousness to moderate disabilities [40]. The main hypothesis anticipates two major effects: (1) a critical decrease in central thalamic outflow secondary to disfacilitation [41] resulting from loss of corticothalamic connections and (2) direct inhibition of central thalamic neurons by disinhibited globus pallidus (GP) neurons as a result of insufficient corticostriatal and thalamostriatal input to the medium spiny neurons (MSNs) of the striatum that require high level of stimulation to reach their firing threshold [42]. Collectively, as a result, the activity across the striatum, central thalamus, and frontal/prefrontal cortices is consequently decreased.

Several studies have found evidence in support of the mesocircuit hypothesis. A recent study compared the metabolic profiles of severely brain-injured patients with DOC, with healthy controls, and identified that metabolism within ventral and association striatum (excluding the sensorimotor portion), as well as in the central thalamus, was reduced in patients, while an increase was observed in the GPi (Fridman et al. [43]—see Fig. 12.2). These reversal profiles in patients as compared to controls in the GPi and the central thalamus give another strong support to the mesocircuit model.

This mesocircuit model provides an economical explanation of the vulnerability of the anterior forebrain in patients with DOC who suffer from widespread

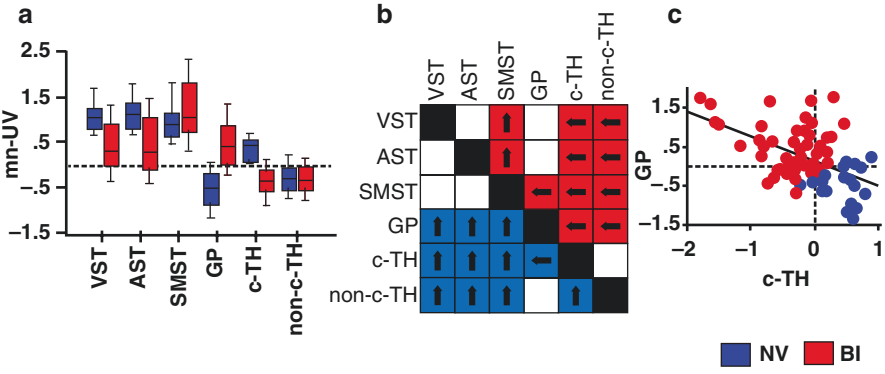

Fig. 12.2 Group data displaying glucose uptake values in deep brain structures measured in healthy controls (in *blue*) and brain-injured subjects (in *red*). (**a**) *Box plot*. A significant reduction in relative glucose metabolism of the ventral striatum (VST), associative striatum (AST), and central thalamus (c-TH) in brain-injured subjects is seen compared with healthy controls. No difference in sensorimotor striatum (SMST) mn-UV is present between healthy controls and brain-injured subjects. A significant increase in GP metabolism is present in the group of BI subjects. (**b**) Significant results are shown in *blue* for healthy controls and *red* for brain-injured patients, whereas *white boxes* denote no significant differences; *arrows* indicate the direction of the significance (i.e., pointing toward the higher mn-UV values). (**c**) Bivariate scattergram demonstrates an inverse linear correlation between glucose metabolic rate of the c-TH (*x*-axis) and the GP (*y*-axis) (From [43])

deafferentation and neuronal cell loss. Interestingly, bulk activation of the anterior forebrain based on the mesocircuit model can explain the effect of several pharmacological interventions, as well as thalamic DBS [34]. An interesting example is zolpidem, a short-acting non-benzodiazepine GABA agonist hypnotic drug that has shown to induce paradoxical responses in some patients with DOC. In a recent study, Chatelle et al. [26] have shown that the recovery of consciousness of three zolpidem responders (i.e., patients who transiently recovered a functional communication under zolpidem) was correlated with an increase in brain metabolism within the dorsolateral prefrontal and mesiofrontal cortices (see Fig. 12.3). Zolpidem could inhibit the GPi by inhibiting the GABAAa-1 subunit, expressed in large quantities in the GPi. This would substitute for the normal inhibition of the GPi from the striatum, hence increasing the thalamic excitatory influence on prefrontal cortices. Additionally, direct excitatory effects at the level of the cortex and striatum likely play a key role in the response [44]. Activation of frontal EEG in zolpidem responders is further consistent with the model and the findings of Chatelle et al. [26]. Interestingly, in all neuroimaging studies investigating the cerebral patterns of zolpidem responders [26, 45, 46], the brain areas showing increased metabolism after zolpidem did not show significant structural lesions, a finding consistent either with the proposal that zolpidem responders have consciousness impairments mainly due to inhibitory functional effects rather than by structural damage [47] or that reduced firing rates produced by disfacilitation are present and that a widening of the dynamic range of these neuronal populations is achieved by release of a circuit-level blockage [44].

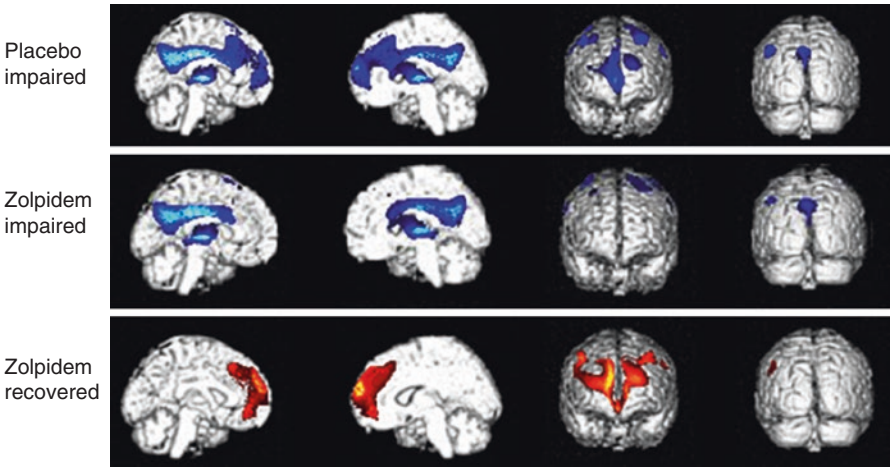

Fig. 12.3 Impaired brain metabolism after placebo and zolpidem intake and areas showing relative recovery after zolpidem. Brain areas showing impaired metabolism (in *blue*) following placebo and zolpidem administration and regions which were impaired following placebo but showed relative recovery of activity after zolpidem intake (in *red*). From left to right, medial right and left view and frontal and posterior view (From [26])

The linkage of the mesocircuit and the frontoparietal model has been specifically supported by both anatomical and functional studies. Loss of structural connections between the thalamus and the posterior medial complex (including posterior cingulate cortex and precuneus, see below) has been statistically correlated with behavioral outcomes after severe brain injuries [48]. Anatomical projections from the central thalamus to the posterior medial cortical regions are strong [49], and a compelling functional correlation has been demonstrated in experimental studies of anesthetized healthy volunteers. Once in a stable plane of anesthesia, pharmacologically induced emergence from deep sedation using physostigmine produced a recovery of consciousness reflected in the ability to engage in command following in some subjects, recovery of command following correlated with co-activation of both the central thalamus and PMC [50]. Collectively, these studies show evidence of an interdependence of the functional integrity of the central thalamus and posterior medial complex and level of consciousness.

In summary, it seems that two important circuit mechanisms are combined in impaired consciousness following a severe brain injury and recovery [35]: (1) a strong link between the level of consciousness (from coma to emergence from MCS) and the preservation of resting metabolism in medial parietal cortex/posterior medial complex (i.e., precuneus, retrosplenial, posterior cortex) and (2) a key role for the central thalamus in regulating the anterior forebrain activation.

Deep Brain Stimulation (DBS)

DBS is widely used to treat several neurological and psychiatric disorders such as motor disorders (e.g., essential tremor, dystonia, Parkinson's disease), chronic pain, or obsessive-compulsive disorders and is FDA approved [51]. Basically, DBS encompasses a pulse generator that sends current to a brain electrode that delivers electrical and magnetic impulses to a targeted brain region. For some diseases, like Parkinson's and dystonia, DBS conceptually "inhibits" the targeted regions, while for other diseases, it has been employed to "excite" brain regions. The detailed underlying mechanisms of DBS are not yet fully understood and mainly depend on the targeted pathological process. At the basic level of initial effect on the brain, however, a primary effect of excitation of axonal action potentials is generally agreed upon outside of very high frequency or amplitude stimulation regimes which may induce conduction blockade [52, 53]. In the context of disorders of consciousness and central thalamic stimulation, direct excitation of projecting thalamocortical afferents is identified as the basic effect through a wide range of basic and clinical neuroscience studies (reviewed in [54]).

DBS in DOC patients aims at stimulating thalamocortical loops across frontostriatal regions responsible for cognitive functions such as attention, memory, language, or executive functions. The intralaminar nuclei were chosen because the central thalamus is suggested to be altered in regard to the pathophysiological mechanisms linked to the brain injury and cellular loss in central thalamus seems to

be particularly associated with DOC patients' level of recovery [40, 55]. Therefore, DBS could facilitate the induction and support the activity in a large network of neurons through the entire brain and thus lead to the recovery of cognitive functions underlined by these networks. In addition, the central thalamus plays a key role in arousal regulation. Indeed, neurons in the intralaminar nuclei of the thalamus are linked and located between the forebrain (involved in premotor shifts of attention and adjustments of vigilance level) and the arousal system in the brainstem [37].

The first DBS studies in DOC, performed between the 1960s and 1990s, failed to demonstrate any clinical improvements related to DBS. More recently, the effects of DBS of the midbrain reticular formation and the median-parafascicular complex were investigated in DOC patients [56]. Eight patients in VS/UWS recovered a response to commands (i.e., MCS+), and four patients in MCS recovered a functional communication (i.e., emerged from MCS). Unfortunately, the protocol did not encompass a controlled arm, and therefore, the exclusive relationship between clinical improvement and DBS cannot be stated.

In 2007, Schiff and collaborators have reported the case of a chronic posttraumatic patient in MCS treated with DBS of thalamic intralaminar nuclei in a double-blind design with recording of several baselines [4]. This was the first study that employed standardized reliable and validated outcome measures (such as the Coma Recovery Scale-Revised—CRS-R [57]) to investigate the efficacy of DBS. Clinically, the patient was in a minimally conscious state for 6 years at a considerably higher level of baseline behavior (CRS-R 19 at initiation of trial) than prior studies (CRS-R estimated ~7–9) and did not show any improvement despite rehabilitation program. DBS was applied bilaterally to the central thalamus and alternated on and off phases in 30-day intervals over 6 months. Intelligible verbalizations and functional object use were directly observed as soon as the stimulator was turned on during the titration period (following continuous stimulation for 18 h) but not within the initial 3-day testing with lower currents and limited times of exposure to stimulation. After a few months of stimulations, responses to command, spontaneous limb movements, oral feeding, and functional communication were objectified during DBS *on* periods. When DBS was turned *off*, behavioral performance decreased significantly but remained above baseline level, suggesting some remnant effects. These functional gains were maintained across the 24-month follow-up phase and for 6 years until the patient's death. Even if more clinical trials are required to confirm these effects in a large population of patients and to better understand the mechanisms of DBS in DOC, these findings are very encouraging for the potential to develop a therapy and the further recovery of some chronic patients with DOC.

Transcranial Direct Current Stimulation (tDCS)

In the past 15 years, many studies have shown that tDCS can modify neuronal excitability and induce behavioral changes in both healthy controls and patients with motor or cognitive dysfunctions [58–61]. Currently, a lot of clinical trials have been

conducted to study the effect of tDCS on poststroke motor and language deficits, in psychiatric disorders, chronic pain, memory impairment, and tinnitus in order to decrease symptoms [62–66]. tDCS represents a safe, cheap, and easy-to-use technique that could be easily integrated in rehabilitation programs. However, its therapeutic effect remains to be more extensively explored [67, 68]. Physiologically, tDCS involves passing a weak (usually ≤2 mA) direct current through the brain between two electrodes, the anode (i.e., excitatory) and the cathode (i.e., inhibitory). By decreasing or increasing the action potential threshold, anodal tDCS enhances excitability, whereas cathodal tDCS reduces it [69]. The formation of the long-lasting aftereffects is not entirely understood but seems to depend on membrane potential changes, modulations of NMDA receptor efficacy, as well as modification of ion channels (e.g., calcium, Liebetanz et al. [70]). In other words, tDCS does not induce the firing of otherwise resting neurons, such as TMS, but rather modulates the spontaneous firing rate of neurons by acting on the membrane potential.

In a first sham-controlled double-blind randomized crossover study, the effect of a single prefrontal tDCS was evaluated in a heterogeneous population of patients with DOC, VS/UWS and MCS, and acute-subacute (<3 months) and chronic, with traumatic or non-traumatic etiologies [71]. At the individual level, tDCS responders were defined as patients who presented a new sign of consciousness (e.g., command following; visual pursuit; recognition, manipulation, or localization of objects; Giacino et al. [72]), after the real tDCS session, that was not present before nor during the sham tDCS session. 13/30 patients in MCS showed a tDCS-related improvement. Two acute (<3 months) patients in VS/UWS out of 25 showed a tDCS response (i.e., showed command following and visual pursuit present after the anodal stimulation not present at baseline or pre- or post-sham tDCS). At group level, a treatment effect, as measured by the CRS-R, was observed in the MCS but not in the VS/UWS patients' group. In addition, no tDCS-related side effects were observed.

These findings appear of critical importance especially if we consider that there are only limited evidence-based pharmacological or non-pharmacological treatment options for severely brain-damaged patients with DOC and particularly in the chronic setting. Indeed, in the aforementioned study, out of the 13 patients in MCS who showed a tDCS response, 5 were included more than 12 months after the acute insult. This suggests that chronic MCS patients, even years after the brain injury, have still the ability to improve and recover some new signs of consciousness. On the other hand, no improvements were observed in patients in VS/UWS, in line with previous studies showing capacity for neural plasticity in patients in MCS rather than VS/UWS [73].

The main limit of this study was the short-term clinical effects of tDCS. Indeed, behavioral improvements were observed for not longer than 2 h from the stimulation. The literature of tDCS seems to convey that the number of sessions is a critical parameter to induce larger effects [74, 75]. As in daily clinical practice longer effects are required, studies using repeated tDCS sessions are warranted to elucidate whether this technique might be a feasible treatment for patients with DOC. To answer that question, another study aiming to evaluate the long-term effect of tDCS

was performed in chronic MCS patients. All participants received sham tDCS, 5 days/week, for 1 week, and anodal tDCS 5 days/week, for 1 week, separated by 1-week period of washout. The level of consciousness (i.e., CRS-R total score) improved after 5 days of tDCS in 56% of the patients included in that study, and the effects lasted 1 week after the end of the stimulations. In addition, a longitudinal increase of the CRS-R total scores was identified for the real session but not for the sham one. Those results suggest that repeated (5 days) anodal left prefrontal tDCS can improve the recovery of consciousness in chronic MCS patients up to 1 week after the last stimulation [76].

In another study, five repeated tDCS sessions (one daily) were performed on ten chronic (>6 months) patients with DOC. The left primary sensorimotor cortex (2 MCS – 3 VS/UWS) or the left DLPF cortex (1 MCS – 4 VS/UWS) was stimulated [77]. All patients in MCS showed clinical improvement immediately after tDCS session, while no effects were observed in patients in VS/UWS, in accordance with the previous tDCS study [71].

Using multimodal neuroimaging analyses, the previously described subgroup of tDCS responders (Thibaut et al. [71]) has been characterized. A common pattern of metabolic gray matter preservation was observed in tDCS responders as compared to nonresponders. This study showed that the transient improvement of signs of consciousness following tDCS seems to require gray matter integrity and/or residual metabolic activity in three brain regions: (1) the medial prefrontal cortex (encompassing the DLPFC, stimulated area), (2) the precuneus, and (3) the thalamus (see Fig. 12.4).

The residual brain metabolism and preserved gray matter in tDCS responders in the prefrontal cortex, posterior cingulate/precuneus, and thalamus highlight the role played by these structures in the recovery of consciousness. As previously mentioned, PET studies on VS/UWS patients identified metabolic impairment in the DMN (i.e., medial prefrontal cortex and the posterior cingulate/precuneus), as well as in the lateral frontoparietal regions including the DLPFC, emphasizing their critical role in consciousness recovery processes [19, 20].

The remaining metabolic and structural integrity of the medial prefrontal cortex and the thalamus observed in tDCS responders also supports the key role of these structures in the disturbances of consciousness and corroborates with previous studies showing that the corticothalamic loop has a critical role in consciousness recovery [78], as well as with the mesocircuit model [34, 43].

Which Technique to Choose?

As regard to the published tDCS studies on DOC patients, it is worth to stress that tDCS seems to be a safe device. Indeed, so far, no severe side effects were observed, even considering that many of these patients had severe brain injuries with widespread lesion possibly involving the stimulated areas. Moreover, although it is well known that brain-injured patients are more vulnerable to epileptic seizure, and some

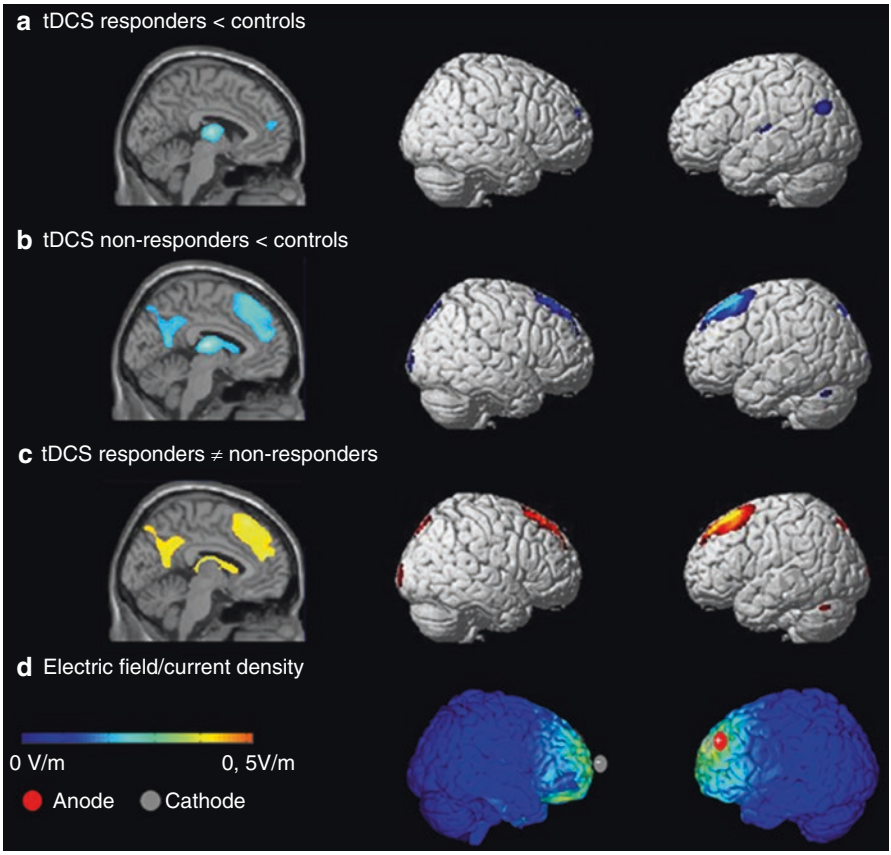

Fig. 12.4 Positron emission tomography (PET). Brain areas showing hypometabolism (in *blue*), as compared to controls, in patients in a minimally conscious state (FEW corrected): (**a**) 8 tDCS responders and (**b**) 13 nonresponders. (**c**) Regions with less hypometabolism in responders as compared to nonresponders (in *red*). (**d**) Theoretical tDCS-induced electric fields. Note that behavioral responsiveness to short duration left dorsolateral prefrontal cortex (DLPFC) tDCS correlates with less impaired metabolism in the areas presumed to be stimulated by tDCS (left DLPFC and mesiofrontal cortices) but also of distant cortical (precuneus) and subcortical (thalamus) regions (From [25])

of them were even under an epileptic treatment due to previous seizures, no seizures as side effects were observed.

On the other hand, DBS exposes the patient to several more risks due to the brain surgery than tDCS but can stimulate the brain centrally in systems evolved to have far-reaching and powerful modulatory effects. In most cases, the postoperative side effects of DBS are limited. It should also be noted that the use of DBS is only investigational and even the study inclusion criteria to receive this stimulation were very strict such that the number of patients likely to be eligible for this approach will be limited.

DBS as compared to tDCS, by stimulating the thalamus, can directly activate the thalamocortical connectivity, which has a critical role for consciousness recovery [35, 78], while tDCS can only directly stimulate cortico-cortical and corticothalamic connectivity. Though activation of the entire network is expected for both techniques to varying degrees, neurons in the central thalamus are specialized for broad activation across the entire frontostriatal system as recently demonstrated using fiberoptic optogenetic activation techniques coupled to functional magnetic resonance imaging [80]. Therefore, DBS might induce more significant clinical improvements than tDCS. Other advantages of DBS are the continuous effect and the permanent stimulation of patients' brain. Indeed, since the stimulator is placed and stays implanted for several years, it does not need to be repeatedly applied in order to induce long-term clinical effects, while for tDCS, repeating the stimulation daily seems to be necessary to induce prolonged behavioral improvements. In addition, since tDCS needs to be repeatedly performed, it requires more human resources, which might be an issue; even tDCS stays a relatively inexpensive and user-friendly technique.

Consistency with the Mesocircuit Model

Interestingly, tDCS and DBS protocols that have been shown to induce promising results on consciousness recovery in DOC patients were focusing on brain areas which are part of the mesocircuit frontoparietal model. Indeed, DLPFC tDCS increases neuronal excitability of the prefrontal cortex, while DBS directly stimulates the central thalamus. These observations are in line with the study of Laureys et al. where a recovery of the connectivity between the thalamus and the frontal area was detected in patients who spontaneously regain consciousness from a vegetative state [78]. Furthermore, it is well known that prefrontal areas are critical in cognitive processes [79], and, more recently, it has been shown that stimulating this regions, even in an noninvasive way, seems to improve signs of consciousness of acute and chronic patients with DOC, though at a lower level as compared to central thalamus DBS. As schematized in Fig. 12.1, this mesocircuit model, by integrating this fronto-striato-thalamic loop, efficiently predicts both the impact of central thalamic DBS and prefrontal tDCS and the effects of a variety of specific pharmacological interventions known to be, in some cases, effective in improving behavioral responsiveness in severely brain-injured patients. In addition, it highlights once more the critical role of the thalamus and its connectivity with the frontal areas for consciousness recovery.

Conclusion

The aforementioned neuromodulation techniques, namely, DBS and tDCS, are thought to excite mainly forebrain regions and restore the connectivity between the thalamus and prefrontal cortex. Depending on patients specificities (e.g., damaged

brain areas), one of these techniques could be tested to improve patients' signs of consciousness and recovery. It would also be interesting to investigate if tDCS responsiveness could be a predictor of DBS efficacy, since both neuromodulation techniques are involved in the fronto-striato-thalamic loop, while tDCS is clearly less invasive than DBS.

Understanding the neural mechanisms of consciousness recovery will help neuroscientists and clinicians to develop new therapeutic options to stimulate the recovery of higher levels of functioning. On the other hand, deepening our knowledge on the mechanisms of how neuromodulation therapies work might help to understand the phenomena occurring in the process of consciousness recovery.

In the years to follow, more work has to be done to strengthen our understanding of the mechanisms of and potential treatments to promote the recovery of consciousness in patients with DOC. This will help improve daily care, comfort, and rehabilitation in this population in acute as well as in chronic stages.

Acknowledgments The authors thank the Belgian American Educational Foundation (AT) and the Jerold B. Katz Foundation (NDS).

References

1. Voss HU, Uluc AM, Dyke JP, et al. Possible axonal regrowth in late recovery from the minimally conscious state. J Clin Invest. 2006;116:2005–11. doi:10.1172/JCI27021.
2. Estraneo A, Moretta P, Loreto V, et al. Late recovery after traumatic, anoxic, or hemorrhagic long-lasting vegetative state. Neurology. 2010;75:239–45. doi:10.1212/WNL.0b013e3181e8e8cc.
3. Bruno M-A, Ledoux D, Vanhaudenhuyse A, et al. Prognosis of patients with altered state of consciousness. Coma Disord Conscious. 2012; doi:10.1007/978-1-4471-2440-5_2.
4. Schiff ND, Giacino JT, Kalmar K, et al. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. Nature. 2007;448:600–3. doi:10.1038/nature06041.
5. Schnakers C, Hustinx R, Vandewalle G, et al. Measuring the effect of amantadine in chronic anoxic minimally conscious state. J Neurol Neurosurg Psychiatry. 2008;79:225–7. doi:10.1136/jnnp.2007.124099.
6. Giacino JT, Whyte J, Bagiella E, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. N Engl J Med. 2012;366:819–26. doi:10.1056/NEJMoa1102609.
7. Fridman EA, Calvar J, Bonetto M, et al. Fast awakening from minimally conscious state with apomorphine. Brain Inj. 2009;23:172–7. doi:10.1080/02699050802649662.
8. Sara M, Sacco S, Cipolla F, et al. An unexpected recovery from permanent vegetative state. Brain Inj. 2007;21:101–3. doi:10.1080/02699050601151761.
9. Whyte J, Rajan R, Rosenbaum A, et al. Zolpidem and restoration of consciousness. Am J Phys Med Rehabil. 2014;93:101–13. doi:10.1097/PHM.0000000000000069.
10. Thonnard M, Gosseries O, Demertzi A, et al. Effect of zolpidem in chronic disorders of consciousness: a prospective open-label study. Funct Neurol. 2014;28:259–64.
11. Jox RJ, Bernat JL, Laureys S, Racine E. Disorders of consciousness: responding to requests for novel diagnostic and therapeutic interventions. Lancet Neurol. 2012;11:732–8. doi:10.1016/S1474-4422(12)70154-0.
12. Laureys S, Lemaire C, Maquet P, et al. Cerebral metabolism during vegetative state and after recovery to consciousness. J Neurol Neurosurg Psychiatry. 1999;67:121.
13. Laureys S, Goldman S, Phillips C, et al. Impaired effective cortical connectivity in vegetative state: preliminary investigation using PET. Neuroimage. 1999;9:377–82. doi:10.1006/nimg.1998.0414.

14. Beuthien-Baumann B, Handrick W, Schmidt T, et al. Persistent vegetative state: evaluation of brain metabolism and brain perfusion with PET and SPECT. Nucl Med Commun. 2003;24:643–9. doi:10.1097/01.mnm.0000075192.18521.9d.
15. Juengling FD, Kassubek J, Huppertz HJ, et al. Separating functional and structural damage in persistent vegetative state using combined voxel-based analysis of 3-D MRI and FDG-PET. J Neurol Sci. 2005;228:179–84. doi:10.1016/j.jns.2004.11.052.
16. Nakao S, Takata S, Uemura H, et al. Relationship between Barthel Index scores during the acute phase of rehabilitation and subsequent ADL in stroke patients. J Med Investig. 2010;57:81–8.
17. Lull N, Noe E, Lull JJ, et al. Voxel-based statistical analysis of thalamic glucose metabolism in traumatic brain injury: relationship with consciousness and cognition. Brain Inj. 2010;24:1098–107. doi:10.3109/02699052.2010.494592.
18. Silva S, Alacoque X, Fourcade O, et al. Wakefulness and loss of awareness: brain and brainstem interaction in the vegetative state. Neurology. 2010;74:313–20. doi:10.1212/WNL.0b013e3181cbcd96.
19. Vanhaudenhuyse A, Noirhomme Q, Tshibanda LJ, et al. Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. Brain. 2010;133:161–71. doi:10.1093/brain/awp313.
20. Thibaut A, Bruno MA, Chatelle C, et al. Metabolic activity in external and internal awareness networks in severely brain-damaged patients. J Rehabil Med. 2012;44:487–94.
21. D'Esposito M, Aguirre GK, Zarahn E, et al. Functional MRI studies of spatial and nonspatial working memory. Brain Res Cogn Brain Res. 1998;7:1–13.
22. D'Esposito M, Detre JA, Alsop DC, et al. The neural basis of the central executive system of working memory. Nature. 1995;378:279–81. doi:10.1038/378279a0.
23. Devinsky O, D'Esposito M. Neurology of cognitive and behavioural disorders. Oxford: Oxford University; 2004.
24. Lieberman MD. Social cognitive neuroscience: a review of core processes. Annu Rev Psychol. 2007;58:259–89. doi:10.1146/annurev.psych.58.110405.085654.
25. Thibaut A, Di Perri C, Chatelle C, et al. Clinical response to tDCS depends on residual brain metabolism and grey matter integrity in patients with minimally conscious state. Brain Stimul. 2015;8:1116–23. doi:10.1016/j.brs.2015.07.024.
26. Chatelle C, Thibaut A, Gosseries O, et al. Changes in cerebral metabolism in patients with a minimally conscious state responding to zolpidem. Front Hum Neurosci. 2014;8:917. doi:10.3389/fnhum.2014.00917.
27. Boly M, Tshibanda L, Vanhaudenhuyse A, et al. Functional connectivity in the default network during resting state is preserved in a vegetative but not in a brain dead patient. Hum Brain Mapp. 2009;30:2393–400. doi:10.1002/hbm.20672.
28. Silva S, de Pasquale F, Vuillaume C, et al. Disruption of posteromedial large-scale neural communication predicts recovery from coma. Neurology. 2015;85:2036–44. doi:10.1212/WNL.0000000000002196.
29. Raichle ME, Snyder AZ. A default mode of brain function: a brief history of an evolving idea. Neuroimage. 2007;37:1083–9. doi:10.1016/j.neuroimage.2007.02.041.
30. Laureys S, Boly M, Maquet P. Tracking the recovery of consciousness from coma. J Clin Invest. 2006;116:1823–5. doi:10.1172/JCI29172.
31. Crone C, Nielsen J, Petersen N, et al. Disynaptic reciprocal inhibition of ankle extensors in spastic patients. Brain. 1994;117(Pt 5):1161–8.
32. Crone JS, Schurz M, Höller Y, et al. Impaired consciousness is linked to changes in effective connectivity of the posterior cingulate cortex within the default mode network. Neuroimage. 2015;110:101–9. doi:10.1016/j.neuroimage.2015.01.037.
33. Lant ND, Gonzalez-Lara LE, Owen AM, Fernández-Espejo D. Relationship between the anterior forebrain mesocircuit and the default mode network in the structural bases of disorders of consciousness. Neuroimage Clin. 2016;10:27–35. doi:10.1016/j.nicl.2015.11.004.

34. Schiff ND. Recovery of consciousness after brain injury: a mesocircuit hypothesis. Trends Neurosci. 2010;33:1–9. doi:10.1016/j.tins.2009.11.002.
35. Laureys S, Schiff ND. Coma and consciousness: paradigms (re)framed by neuroimaging. Neuroimage. 2012;61:478–91. doi:10.1016/j.neuroimage.2011.12.041.
36. Giacino JT, Fins JJ, Laureys S, Schiff ND. Disorders of consciousness after acquired brain injury: the state of the science. Nat Rev Neurol. 2014;10:99–114. doi:10.1038/nrneurol.2013.279.
37. van der Werf YD, Witter MP, Groenewegen HJ. The intralaminar and midline nuclei of the thalamus. Anatomical and functional evidence for participation in processes of arousal and awareness. Brain Res Rev. 2002;39:107–40. doi:10.1016/S0165-0173(02)00181-9.
38. Schiff ND. Central thalamic contributions to arousal regulation and neurological disorders of consciousness. Ann N Y Acad Sci. 2008;1129:105–18. doi:10.1196/annals.1417.029.
39. Mair RG, Onos KD, Hembrook JR. Cognitive activation by central thalamic stimulation: the Yerkes–Dodson law revisited. Dose Response. 2011;9:313–31. doi:10.2203/dose-response.10-017.Mair.
40. Maxwell WL, MacKinnon MA, Smith DH, et al. Thalamic nuclei after human blunt head injury. J Neuropathol Exp Neurol. 2006;65:478–88. doi:10.1097/01.jnen.0000229241.28619.75.
41. Gold L, Lauritzen M. Neuronal deactivation explains decreased cerebellar blood flow in response to focal cerebral ischemia or suppressed neocortical function. Proc Natl Acad Sci U S A. 2002;99:7699–704. doi:10.1073/pnas.112012499.
42. Grillner S, Hellgren J, Menard A, et al. Mechanisms for selection of basic motor programs—roles for the striatum and pallidum. Trends Neurosci. 2005;28:364–70. doi:10.1016/j.tins.2005.05.004.
43. Fridman EA, Beattie BJ, Broft A, et al. Regional cerebral metabolic patterns demonstrate the role of anterior forebrain mesocircuit dysfunction in the severely injured brain. Proc Natl Acad Sci U S A. 2014;111:6473–8. doi:10.1073/pnas.1320969111.
44. Williams ST, Conte MM, Goldfine AM, et al. Common resting brain dynamics indicate a possible mechanism underlying zolpidem response in severe brain injury. Elife. 2013;2:e01157. doi:10.7554/eLife.01157.
45. Brefel-Courbon C, Payoux P, Ory F, et al. Clinical and imaging evidence of zolpidem effect in hypoxic encephalopathy. Ann Neurol. 2007;62:102–5. doi:10.1002/ana.21110.
46. Clauss RP, Güldenpfennig WM, Nel HW, et al. Extraordinary arousal from semi-comatose state on zolpidem. A case report. S Afr Med J. 2000;90:68–72.
47. Shames JL, Ring H. Transient reversal of anoxic brain injury-related minimally conscious state after zolpidem administration: a case report. Arch Phys Med Rehabil. 2008;89:386–8. doi:10.1016/j.apmr.2007.08.137.
48. Fernandez-Espejo D, Soddu A, Cruse D, et al. A role for the default mode network in the bases of disorders of consciousness. Ann Neurol. 2012;72:335–43. doi:10.1002/ana.23635.
49. Buckwalter JA, Parvizi J, Morecraft RJ, Van Hoesen GW. Thalamic projections to the posteromedial cortex in the macaque. J Comp Neurol. 2008;507:1709–33. doi:10.1002/cne.21647.
50. Xie G, Deschamps A, Backman SB, et al. Critical involvement of the thalamus and precuneus during restoration of consciousness with physostigmine in humans during propofol anaesthesia: a positron emission tomography study. Br J Anaesth. 2011;106:548–57. doi:10.1093/bja/aeq415.
51. Olanow CW, Brin MF, Obeso JA. The role of deep brain stimulation as a surgical treatment for Parkinson's disease. Neurology. 2000;55:S60–6.
52. McIntyre CC, Savasta M, Kerkerian-Le Goff L, Vitek JL. Uncovering the mechanism(s) of action of deep brain stimulation: activation, inhibition, or both. Clin Neurophysiol. 2004;115:1239–48. doi:10.1016/j.clinph.2003.12.024.
53. Agnesi F, Johnson MD, Vitek JL. Deep brain stimulation. How does it work? Handb Clin Neurol. 2013;116:39–54. doi:10.1016/B978-0-444-53497-2.00004-8.
54. Shah SA, Schiff ND. Central thalamic deep brain stimulation for cognitive neuromodulation—a review of proposed mechanisms and investigational studies. Eur J Neurosci. 2010;32:1135–44. doi:10.1111/j.1460-9568.2010.07420.x.

55. Adams JH, Graham DI, Jennett B. The neuropathology of the vegetative state after an acute brain insult. Brain. 2000;123(Pt 7):1327–38.
56. Yamamoto T, Kobayashi K, Kasai M, et al. DBS therapy for the vegetative state and minimally conscious state. Acta Neurochir Suppl. 2005;93:101–4.
57. Giacino JT, Kalmar K, Whyte J. The JFK coma recovery scale-revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil. 2004;85:2020–9.
58. Boggio PS, Ferrucci R, Rigonatti SP, et al. Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. J Neurol Sci. 2006;249:31–8. doi:10.1016/j.jns.2006.05.062.
59. Ferrucci R, Mameli F, Guidi I, et al. Transcranial direct current stimulation improves recognition memory in Alzheimer disease. Neurology. 2008;71:493–8. doi:10.1212/01.wnl.0000317060.43722.a3.
60. Kang EK, Kim DY, Paik NJ. Transcranial direct current stimulation of the left prefrontal cortex improves attention in patients with traumatic brain injury: a pilot study. J Rehabil Med. 2012;44:346–50. doi:10.2340/16501977-0947.
61. Nelson JT, McKinley RA, Golob EJ, et al. Enhancing vigilance in operators with prefrontal cortex transcranial direct current stimulation (tDCS). Neuroimage. 2012; doi:10.1016/j.neuroimage.2012.11.061.
62. Antal A, Terney D, Kuhnl S, Paulus W. Anodal transcranial direct current stimulation of the motor cortex ameliorates chronic pain and reduces short intracortical inhibition. J Pain Symptom Manag. 2010;39:890–903. doi:10.1016/j.jpainsymman.2009.09.023.
63. Baker JM, Rorden C, Fridriksson J. Using transcranial direct-current stimulation to treat stroke patients with aphasia. Stroke. 2010;41:1229–36. doi:10.1161/STROKEAHA.109.576785.
64. Frank E, Schecklmann M, Landgrebe M, et al. Treatment of chronic tinnitus with repeated sessions of prefrontal transcranial direct current stimulation: outcomes from an open-label pilot study. J Neurol. 2012;259:327–33. doi:10.1007/s00415-011-6189-4.
65. Loo CK, Alonzo A, Martin D, et al. Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. Br J Psychiatry. 2012;200:52–9. doi:10.1192/bjp.bp.111.097634.
66. Zaehle T, Sandmann P, Thorne JD, et al. Transcranial direct current stimulation of the prefrontal cortex modulates working memory performance: combined behavioural and electrophysiological evidence. BMC Neurosci. 2011;12:2. doi:10.1186/1471-2202-12-2.
67. George MS, Padberg F, Schlaepfer TE, et al. Controversy: repetitive transcranial magnetic stimulation or transcranial direct current stimulation shows efficacy in treating psychiatric diseases (depression, mania, schizophrenia, obsessive-compulsive disorder, panic, posttraumatic stress disorder). Brain Stimul. 2009;2:14–21. doi:10.1016/j.brs.2008.06.001.
68. Nitsche MA, Cohen LG, Wassermann EM, et al. Transcranial direct current stimulation: state of the art 2008. Brain Stimul. 2008;1:206–23. doi:10.1016/j.brs.2008.06.004.
69. Nitsche MA, Seeber A, Frommann K, et al. Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. J Physiol. 2005;568:291–303. doi:10.1113/jphysiol.2005.092429.
70. Liebetanz D, Nitsche MA, Tergau F, Paulus W. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain. 2002;125:2238–47.
71. Thibaut A, Bruno MA, Ledoux D, et al. tDCS in patients with disorders of consciousness: sham-controlled randomised double blind study. Neurology. 2014;82:1112–8.
72. Giacino JT, Ashwal S, Childs N, et al. The minimally conscious state: definition and diagnostic criteria. Neurology. 2002;58:349–53.
73. Monti MM. Cognition in the vegetative state. Annu Rev Clin Psychol. 2012;8:431–54. doi:10.1146/annurev-clinpsy-032511-143050.
74. Castillo-Saavedra L, Gebodh N, Bikson M, et al. Clinically effective treatment of fibromyalgia pain with high-definition transcranial direct current stimulation: phase II open-label dose optimization. J Pain. 2016;17:14–26. doi:10.1016/j.jpain.2015.09.009.

75. Brunoni AR, Valiengo L, Baccaro A, et al. The sertraline vs. electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. JAMA Psychiat. 2013;70:383–91. doi:10.1001/2013.jamapsychiatry.32.
76. Thibaut A, Bruno MA, Wannez S, et al. Long term effect of repeated tDCS in minimally conscious patients. Submitted.
77. Angelakis E, Liouta E, Andreadis N, et al. Transcranial direct current stimulation effects in disorders of consciousness. Arch Phys Med Rehabil. 2014;95:283–9. doi:10.1016/j.apmr.2013.09.002.
78. Laureys S, Faymonville ME, Luxen A, et al. Restoration of thalamocortical connectivity after recovery from persistent vegetative state. Lancet. 2000;355:1790–1.
79. Dehaene S, Sergent C, Changeux JP. A neuronal network model linking subjective reports and objective physiological data during conscious perception. Proc Natl Acad Sci U S A. 2003;100:8520–5. doi:10.1073/pnas.1332574100.
80. Liu J, Lee HJ, Weitz AJ, Fang Z, Lin P, Choy M, Fisher R, Pinskiy V, Tolpygo A, Mitra P, Schiff N, Lee JH. Frequency-selective control of cortical and subcortical networks by central thalamus. Elife. 2015 Dec 10;4:e09215. doi:10.7554/eLife.09215.

Chapter 13
The Ethics in the Management of Patients with Disorders of Consciousness

A. Demertzi

Abstract The ethical issues accrued from the study and management of patients with disorders of consciousness are variant and multifaceted. The medical, public and legal controversies are partly shaped by how different people think about pain perception and end of life. Uniform ethical frameworks need to be shaped in order to guide clinicians and caregivers in terms of clinical outcome, prognosis and medical management.

Introduction

The introduction of the mechanical ventilator in the 1950s and the development of intensive care in the 1960s permitted many patients, who would otherwise might have died from apnea, to sustain their vegetative functions and survive their injuries. Paradoxically, in many cases these survivors were nevertheless found to suffer from altered states of consciousness which had never been encountered before [1]. The imminent ethical impact of these profound states of unconsciousness was reflected in the composition of the first bioethical committees discussing the redefinition of life and the concept of therapeutic obstinacy. In 1968 the Ad Hoc Committee of Harvard Medical School published a milestone paper for the redefinition of death as irreversible coma and brain failure [2]. The fact the committee comprised of ten physicians, a theologian, a lawyer and a historian of science, betokened the medical, legal and societal debates that were to follow.

A. Demertzi, Ph.D.
Institut du Cerveau et de la Moelle Epinière (ICM) - Brain and Spine Insititute, Hôpital Pitié-Salpêtrière, 47, bd de l'Hôpital, 75013 Paris, France

Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium
e-mail: a.demertzi@ulg.ac.be

C. Schnakers, S. Laureys (eds.), *Coma and Disorders of Consciousness*,
DOI 10.1007/978-3-319-55964-3_13

Consciousness Can Be Defined Clinically

Confusions and controversies are often a matter of definition. One multifaceted term with divergent connotations is consciousness [3]. For example, in a survey among healthcare professionals and students, it was found that although the majority of participants denied the distinction between consciousness and the brain, more than one-third still regarded mind and brain as separate entities [4]. The way we define consciousness is crucial especially in the clinical setting because it may govern our opinions and eventually our actions. From a clinical viewpoint, consciousness is defined as having two components, wakefulness and awareness [5]. Under this definition, many variant altered states of consciousness may be hosted. The most familiar to us all is the transition from conscious wakefulness to deep sleep: the drowsier we become, the less aware we get of our surroundings and of ourselves. This implies that patients in coma and under anaesthesia are unaware because they cannot be awakened, even after painful stimulation. An exception to the way that these two components are related comes from patients in the so-called vegetative state (VS) or, as most recently defined, in unresponsive wakefulness syndrome (UWS) [6, 7]. Patients in VS/UWS typically open their eyes but never exhibit nonreflex voluntary movements indicating preserved awareness. In 2002, the term minimally conscious state (MCS) was introduced to describe those patients who showed more complex behaviours declarative of awareness, such as visual pursuit, orientation to pain or nonsystematic command following. Importantly, patients in MCS remain unable to communicate their thoughts and feelings [8]. Because these signs of consciousness often are small and fluctuating in time, this condition may be challenging to diagnose and to differentiate from the VS/UWS [9]. This is one of the reasons that assisting technologies, by providing data-driven objective evaluations of consciousness level, are becoming all the more an important source of information that clinicians are often refer to in order to increase their clinical verdict, e.g. [10–13]. It has been suggested that once conscious awareness has been identified and its quality is estimated in a noncommunicating patient, this may well be a good reason to preserve life-sustaining aids [14]. However, the moral significance of preserved consciousness has been questioned on the grounds that it may not always be in patients' best interest to continue a severely handicapped life [15]. Below we will see what kind of ethical concerns may arise during the medical management of DOC patients and how healthcare workers and next of kin consider these issues.

Emerging Ethical Issues About Pain

The day-to-day needs of patients with DOC are exclusively covered by the healthcare providers and patients' families and next of kin. Patients with DOC cannot communicate their feelings or experience, but it is not unusual that during cares, they will exhibit facial expressions and/or vocalize. Such behaviours can be

confusing for the carers as they might consider them as reactions to pain. As defined by the Multi-Society Task Force on PVS, "pain and suffering refer to the unpleasant experiences that occur in response to stimulation of peripheral nociceptive receptors and their peripheral and central afferent pathways or that they may emanate endogenously from the depths of human self-perception" [16]. Thus, pain constitutes a conscious experience with a physical (nociception) and a psychological counterpart (suffering). This also suggests that nociception by itself is not sufficient to cause suffering. Such differentiation is reflected on how clinicians perceive pain in these patients. According to surveyed attitudes among healthcare professionals, there was a unanimous support that patients in MCS (96%) perceive pain, whereas opinions were less clear for the VS/UWS (56%) [17]. Considering these results on varying beliefs about pain perception in DOC, physicians and healthcare workers' views on analgesia and symptom management may also be affected. Since nearly half of the surveyed doctors expressed that VS/UWS patients do not feel pain, they could be expected to act accordingly, for instance, by not providing analgesic medication in these patients during cares. How, then, are clinicians supposed to infer whether a patient in VS/UWS or MCS feels pain and that she/he may be suffering? At the patient's bedside, we are limited to evaluate the behavioural responsiveness to pain: if patients do not show signs of voluntary movement, such as to localize the source of noxious stimulus, it can be concluded they do not experience pain. Recently, the Nociception Coma Scale-Revised [18] was introduced as a more specific measure of pain in patients with DOC. However, the absence of a behavioural response cannot be taken as a proof of the absence of conscious perception [19]. As such, the inference of pain and suffering merely by observing behavioural responses may be misleading. This can be dramatically illustrated in the case of conscious but paralysed locked-in syndrome (LIS) patients, who, when in a total LIS, they are unable to use motor function to respond to painful stimulation [20]. Importantly, patients with DOC will show restricted motor reactions to noxious stimulation, either stereotyped extension denoting "decerebration" or stereotyped flexion denoting "decortication". In addition, they will frequently show increased arousal levels (evidenced by opening or widening of the eyes), quickening of breathing, increased heart rate and blood pressure or grimace-like or crying-like behaviours. As all these abilities are also seen in infants with anencephaly [21], they are considered to be of subcortical origin and not necessarily reflecting conscious perception of pain. Functional neuroimaging studies may assist in the formulation of a clearer clinical picture as regards pain perception in DOC. By means of positron emission tomography (PET), it has been shown that patients in VS/UWS exhibited cerebral processing of the incoming noxious stimulus (activation of primary somatosensory areas), but the observed neural activity was isolated and disconnected from higher-order associative brain areas which are considered necessary for conscious perception [22]. Critically, the results were very different for patients in MCS, as these patients showed cerebral activation in a more widespread network of regions similar to that of healthy controls, suggesting a potential pain perception these patients [23].

Taken together, these studies suggest that pain perception in DOC is an issue which may govern their actions. For instance, clinicians may decide not to provide

analgesic medication in VS/UWS patients during care or during the dying process after withdrawal of artificial hydration and nutrition [24], the latter on the grounds that these patients are deployed from experiencing suffering from hunger or thirst [25]. But would clinicians' views on pain perception influence their attitudes on end of life? It might be, for example, that caregivers would opt for an irreversible decision after the principle of non-maleficence (i.e. "do not harm"), to spare their patient from unnecessary suffering. According to a European survey, this does not seem to be the case. Among healthcare professions, treatment withdrawal for chronic VS/UWS was supported more (77%) when respondents considered that these patients do not feel pain [26]. Hence, it seems that clinicians made their decision according to formal guidelines on pain management in the end of life. In particular, the Multi-Society Task Force on PVS negates the possibility that patients in VS/UWS experience pain. In the same line is the Royal College of Physicians, which nevertheless recommends the administration of sedatives after treatment withdrawal, targeting at the elimination of a remote possibility of suffering [27]. According to the same survey, albeit less pronounced as compared to VS/UWS, the opinions for chronic MCS were similar: only 29% of respondents supported treatment withdrawal when they thought that these patients feel pain, and 38% considered treatment limitation options when they thought that MCS patient did not feel pain [26]. Therefore, it may be that clinicians feel more comfortable with treatment limitation options once they assure that the potential risk for pain perception is as low as possible. At the same time, it might be that respondents equalized pain perception with preserved awareness. In that respect, the potential existence of pain would give a strong reason to preserve life than opt for treatment limitation options.

Emerging Ethical Issues About End of Life

In the intensive care, medical doctors and assisting staff are confronted daily with situations where clinical decisions are critical, such as continuing or withdrawing life-sustaining treatment. Treatment limitations can be viewed as having two directions depending on whether the decision is made preoperatively or after an intervention [28]. In the former case, it may come as a refusal of cardiopulmonary resuscitation (CPR) in case of cardiopulmonary arrest. In the latter case, it most usually comes as a decision to withdraw treatment, such as the artificial respirator or artificial nutrition and hydration (ANH). CPR is almost automatically performed as an emergency therapy in order to restore heartbeat and ceased breathing, unless the patient or the legal representative has refused it in advance in a form of Do Not Resuscitate (DNR) order. Nevertheless, it should be noted that DNRs do not necessarily prohibit other therapies. They rather authorize the physician to act on this specific manner of therapy [29]. When the clinical condition of a patient has been stabilized and denoted as irreversible, decisions about ANH limitation may come into play. From a bioethical standpoint, withdrawing ANH is comparable to withdrawing mechanical ventilation, even if emotionally they may be perceived

differently. In the intensive care, the majority of deaths are the result of a medical decision to withhold or withdraw treatment [30]. Such decisions are evidence-based and rely on validated clinical or paraclinical markers of bad outcome (e.g. for anoxic coma see [31]). Despite the controversy as to whether ANH constitutes a medical treatment [32] and thus should never be withdrawn from patients [33], most of the Anglo-Saxon medical community would agree with its being a medical therapy which can be refused by patients and surrogate decision-makers [34]. Such decisions in the VS/UWS are only justified when a case is denoted as irreversible [27]. To date, guidelines with regard to temporal determination of a definitive outcome in the VS/UWS state that if no recovery is observed within 3 months after a non-traumatic or 12 months after a traumatic accident, the condition of the patient can be denoted as permanent [16].

The controversies around the clinical management at the end of life in DOC patients were reflected in a European survey (n = 2475), where the majority (66%) of healthcare professionals agreed to withdraw treatment from chronic VS/UWS patients, whereas only 28% agreed so for the chronic MCS [35]. Additionally, 82% of the clinicians wished not to be kept alive if they imagined themselves in a chronic VS/UWS, and a similarly high proportion (67%) agreed so if they imagined themselves in a chronic MCS [35]. Geographical region and religion were among the factors that explained most of the variance in the responses. The detected differences between the two states could be due to the existing legal ambiguity around MCS which may have influenced the surveyed participants to differentiate between expressing preferences for self versus others, by implicitly recognizing that the latter could be a step on the slippery slope to euthanasia.

Clinicians' opinions appear much more uniform with regard to brain death [36]. As mentioned earlier, the Ad Hoc Committee of the Harvard Medical School went on to the redefinition of death as a consequence of the technological advancements in the intensive care, where patients could sustain their severe injuries but maintain the function of vital organs [2]. It was, hence, possible to dissociate between cardiac, respiratory and brain functions which in turn required an alternative definition of death, moving from a cardiorespiratory towards a neurocentric formulation (i.e. irreversible coma). According to the latter, death can be viewed either as death of the whole brain or of the brainstem or as neocortical [37]. The first two are defined as the irreversible cessation of the organism as a whole, differing in their anatomical interpretation [38], whereas the last solely requires the irreversible loss of the capacity of consciousness and social interaction but has never convinced medical or legal scholars. The main utility of the introduction of brain death is that it permitted vital organ procurement for transplantation with the application of ethical restrictions, such as the dead donor rule (i.e. a patient has to be declared dead before the removal of life-sustaining organs). Based on the neocortical definition of death, however, both patients in VS/UWS and MCS can be declared dead. It has been argued that the neocortical definition is conceptually inadequate and practically unfeasible, especially in lack of a complete understanding of higher-order conscious functioning. Hence, patients with DOC are not dead [30], and organ donation options in these patients should be excluded since they violate the dead donor rule [39].

Legal Issues in Disorders of Consciousness

Disorders of consciousness have posed not only medical challenges, but in many cases they required the mediation of legal authorities in order to regulate ambiguous and controversial issues, such as end-of-life decisions. When end-of-life wishes have not been earlier formulated in the form of an advanced directive (i.e. written statement completed by a competent person in anticipation of her/his future incompetence, expressing personal treatment preferences and formal surrogacy appointment), then a surrogate decision-maker is eligible to take responsibility of the patient's clinical management. The way the legal representative should act on behalf of the patient is a progressive one: (a) the surrogate should first attempt to follow the wishes of the patient as closely as possible the way they were expressed before the accident, either orally or in the form of advance directives; (b) when the wishes are unknown and an advance directive is not available, the surrogate decision-maker should try to reproduce the patients' preferences based on their history and personal values; (c) when this is not possible, the decisions should rely on more objective markers that determine the patients' best interest (e.g. likelihood of recovery, pain management, impact on family) [28, 40]. The proxy decision-maker should mediate trying to maximize patients' self-determination and protect their interests on the principles of beneficence and non-maleficence.

The use of advance directives could also be considered as a means to regulate cost savings in the end of life. Once the wishes of a terminal patient are known, care can be taken as to constrain extraordinary means and spare the available resources on other urgent cases. However, no such rationale corresponds to the reality, and advance directives, together with hospice care and the elimination of futile care, have not contributed to the effective regulation of the economics of dying [41]. Treatment resources are not unlimited, and despite care for a good death, sometimes physicians need to do with the means they have available. The allocation of resources and the economics at the end of life have not yet been fully determined for DOC patients. In intensive care medicine, some unwritten rules can facilitate decisions as to who is to be treated, like the "first come" principle or "who will most likely benefit from the intensive care" [42]. However, for chronic DOC cases, information on resource allocation often is lacking. This may be due to the nature of chronic VS/UWS and MCS patients. These are severely brain-damaged patients for whom the dilemma on treating becomes crucial either because treatments are not guaranteed as successful (i.e. the condition is too bad to be treated) or unkind (i.e. the quality of life of those surviving is not acceptable) which may lead to an unwise way to allocate the available resources.

The legal provisions concerning the end-of-life issues in DOC differ from country to country. In the United States, where a patient-centred medical framework has been adopted, the patient is allowed to participate in the regulation of her/his own course of the disease. In the case of DOC, legal representatives in close collaboration with the clinical staff and in line with the patients' previously expressed wishes may decide together about the long-term care of irreversibly comatose patients.

There are times, however, when conflict of interests arises while making such decisions either between family and physicians, such as in the Quinlan case [43] or among family members, like the Schiavo case [44]. As most often such cases require the mediation of the court, they may have a wider publicity where the public opinion can come into play and may lead to societal movements on pro-life versus right-to-die action groups [45]. In Europe there are more subtle differences in the way treatment limitation is perceived, especially between Northern (more right-to-die oriented) and Southern European countries (more pro-life positioned) [35]. In general, decisions for treatment limitation, usually concerning ANH, need to be taken after reference to the court. Exceptions are the Netherlands, Belgium, Switzerland and Scandinavian countries where no court mediation is needed for limiting treatment in DOC patients [46].

Conclusions

Early since disorders of consciousness appeared in the clinical setting, clinicians, scholars, theologians and ethicists began to wonder what it is like to be in a state of profoundly disturbed consciousness. Are these unresponsive patients in pain, and can they even suffer from it? How can their quality of life be assessed? More importantly, is a life in such severely restricted conditions worth living? Controversies of these kinds mainly stem from how different people regard indefinite survival in disorders of consciousness. Despite the general view that quality of life is diminished in disease as a result of limited capacities to functionally engage in everyday living, these attitudes are formulated from a third-person perspective. Consequently, only rough estimations about what it is like to be in such a situation can be made. For instance, an analysis of public media reports on Terri Schiavo revealed that in some cases, the patient was described as feeling discomfort, which was incompatible with her clinical state [47]. This implies that nonmedical individuals, whose opinions are supposedly represented by media reports, may be biased towards residual cognitive function of patients with consciousness alterations. Such bias could be attributed to the fact that patients' quality of life evaluations are made from the perspective of healthy individuals who tend to underestimate patients' subjective well-being [48]. Indeed, we recently showed that patients in LIS expressed a positive subjective quality of life contrary to what could be expected in this condition [49]. As mentioned above, patients with LIS do not suffer from disorders of consciousness. As such, LIS patients constitute a nice control population for patients with disorders of consciousness due to their resemblance in terms of physical disability and possibly common history, such like LIS patients can have been in comatose-like states. Interestingly, when healthcare professionals were asked whether they wished to be kept alive if imagined themselves in this condition, 56% did not wish so despite the majority (75%) opposing to treatment withdrawal in LIS [50]. When LIS was compared to DOC, more respondents endorsed that being in a LIS was worse than being in a VS/UWS state or MCS (59%). Such studies suggest

that personal characteristics mediate opinions about DOC and LIS. The dissociation between personal preferences and general opinions underlies the difference in perspective in disability and implies that healthy persons who are not in direct contact with this patient population can have distorted pictures as to what is life in these severely constrained situations. By means of functional neuroimaging and electrophysiology, however, the grey zones of unconsciousness start getting illuminated [51]. In should be noted that although these developments are promising to detect and evaluate preserved awareness in these conditions, they need to be translated in clinical practice. For example, in terms of treatment planning, such as pain management and end-of-life decision-making, patients with disorders of consciousness are now offered the possibility to express their preferences by means of brain-computer interfaces. What remains to be clarified is the degree to which such indirect responses can be considered reliable and worthy of legal representation. Uniform ethical frameworks need to be shaped in order to guide clinicians and caregivers in terms of clinical outcome, prognosis and medical management.

References

1. Laureys S, Boly M. What is it like to be vegetative or minimally conscious? Curr Opin Neurol. 2007;20(6):609–13.
2. Ad Hoc Committee of the Harvard Medical School. A definition of irreversible coma. JAMA. 1968;205(6):337–40.
3. Zeman A. Consciousness. Brain. 2001;124:1263–89.
4. Demertzi A, Liew C, Ledoux D, Bruno MA, Sharpe M, Laureys S, et al. Dualism persists in the science of mind. Ann N Y Acad Sci. 2009;1157:1–9.
5. Posner JB, Saper CB, Schiff ND, Plum F. Plum and Posner's diagnosis of stupor and coma. 4th ed. New York: Oxford University Press; 2007.
6. Jennett B, Plum F. Persistent vegetative state after brain damage: a syndrome in search of a name. Lancet. 1972;299(7753):734–7.
7. Laureys S, Celesia GG, Cohadon F, Lavrijsen J, León-Carrión J, Sannita WG, et al. Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. BMC Med. 2010;8(1):68.
8. Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, et al. The minimally conscious state: definition and diagnostic criteria. Neurology. 2002;58(3):349–53.
9. Schnakers C, Vanhaudenhuyse A, Giacino J, Ventura M, Boly M, Majerus S, et al. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. BMC Neurol. 2009;9:35.
10. Demertzi A, Antonopoulos G, Heine L, Voss HU, Crone JS, de Los Angeles C, et al. Intrinsic functional connectivity differentiates minimally conscious from unresponsive patients. Brain. 2015;138:2619–31.
11. Sitt JD, King J, El Karoui I, Rohaut B, Faugeras F, Gramfort A, et al. Large scale screening of neural signatures of consciousness in patients in a vegetative or minimally conscious state. Brain. 2014;137:2258–70.
12. Stender J, Gosseries O, Bruno M, Charland-verville V, Vanhaudenhuyse A, Demertzi A, et al. Diagnostic precision of PET imaging and functional MRI in disorders of consciousness: a clinical validation study. Lancet Neurol. 2014;6736(14):8–16.

13. Casali AG, Gosseries O, Rosanova M, Boly M, Sarasso S, Casali KR, et al. A theoretically based index of consciousness independent of sensory processing and behavior. Sci Transl Med. 2013;5(198):198ra105.
14. Horne M. Are people in a persistent vegetative state conscious? Monash Bioeth Rev. 2009;28(2):12-1-12.
15. Kahane G, Savulescu J. Brain damage and the moral significance of consciousness. J Med Philos. 2009;34:6–26.
16. The Multi-society Task Force on PVS. Medical aspects of the persistent vegetative state-2. N Engl J Med. 1994;330:1572–9.
17. Demertzi A, Schnakers C, Ledoux D, Chatelle C, Bruno M-A, Vanhaudenhuyse A, et al. Different beliefs about pain perception in the vegetative and minimally conscious states: a European survey of medical and paramedical professionals. Prog Brain Res. 2009;177:329–38.
18. Schnakers C, Chatelle C, Vanhaudenhuyse A, Majerus S, Ledoux D, Boly M, et al. The nociception coma scale: a new tool to assess nociception in disorders of consciousness. Pain. 2010;148(2):215–9.
19. McQuillen MP. Can people who are unconscious or in the 'vegetative state' perceive pain? Issues Law Med. 1991;6(4):373–83.
20. Laureys S, Pellas F, Van Eeckhout P, Ghorbel S, Schnakers C, Perrin F, et al. The locked-in syndrome: what is it like to be conscious but paralyzed and voiceless? Prog Brain Res. 2005;150(5):495–611.
21. The infant with anencephaly. N Engl J Med. 1990;322(10):669–74.
22. Laureys S, Faymonville ME, Peigneux P, Damas P, Lambermont B, Del Fiore G, et al. Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. Neuroimage. 2002;17(2):732–41.
23. Boly M, Faymonville M-E, Schnakers C, Peigneux P, Lambermont B, Phillips C, et al. Perception of pain in the minimally conscious state with PET activation: an observational study. Lancet Neurol. 2008;7(11):1013–20.
24. Fins JJ. Affirming the right to care, preserving the right to die: disorders of consciousness and neuroethics after Schiavo. Palliat Support Care. 2006;4(2):169–78.
25. Ahronheim JC, Gasner MR. The sloganism of starvation. Lancet. 1990;335(8684):278–9.
26. Demertzi A, Racine E, Bruno A, Ledoux D, Gosseries O, Vanhaudenhuyse A, et al. Pain perception in disorders of consciousness: neuroscience, clinical care, and ethics in dialogue. Neuroethics. 2013;6(1):37–50.
27. A report of a working party of the Royal College of Physicians. The vegetative state: guidance on diagnosis and management. Clin Med. 2003;3(3):249–54.
28. Bernat JL. Ethical issues in the perioperative management of neurologic patients. Neurol Clin. 2004;22:457–71.
29. Youngner SJ. Do-not-resuscitate orders: no longer secret, but still a problem. Hastings Cent Rep. 1987;17(1):24–33.
30. Laureys S. Science and society: death, unconsciousness and the brain. Nat Rev Neurosci. 2005;6(11):899–909.
31. Boveroux P, Kirsch M, Boly M, Massion P, Sadzot B, Lambermont B, et al. Evaluation du pronostic neurologique dans les encéphalopathies postanoxiques. Reanimation. 2008;17:613–7.
32. Bernat JL, Beresford HR. The controversy over artificial hydration and nutrition. Neurology. 2006;66(11):1618–9.
33. Rosner F. Why nutrition and hydration should not be withheld from patients. Chest. 1993;104(6):1892–6.
34. Steinbrook R, Lo B. Artificial feeding—solid ground, not a slippery slope. N Engl J Med. 1988;318(5):286–90.

35. Demertzi A, Ledoux D, Bruno M-A, Vanhaudenhuyse A, Gosseries O, Soddu A, et al. Attitudes towards end-of-life issues in disorders of consciousness: a European survey. J Neurol. 2011;258(6):1058–65.
36. Bernat JL. The concept and practice of brain death. Prog Brain Res. 2005;150:369–79.
37. Brierley JB, Graham DI, Adams JH, Simpsom JA. Neocortical death after cardiac arrest. A clinical, neurophysiological, and neuropathological report of two cases. Lancet. 1971;2(7724): 560–5.
38. Bernat JL. Brain death. In: Laureys S, Tononi G, editors. The neurology of consciousness. 1st ed. London: Academic Press; 2009. p. 151–62.
39. Engelhardt K. Organ donation and permanent vegetative state. Lancet. 1998;351(9097): 211–3.
40. Bernat JL. Clinical ethics and the law. In: Ethical issues in neurology. Lippincott Williams & Wilkins; 2002. p. 79–107.
41. Emanuel EJ, Emanuel LL. The economics of dying. The illusion of cost savings at the end of life. N Engl J Med. 1994;330(8):540–4.
42. Jennett B. Resource allocation for the severely brain-damaged. Arch Neurol. 1976;33:595–7.
43. Beresford HR. The Quinlan decision: problems and legislative alternatives. Ann Neurol. 1977;2:74–81.
44. Quill TE. Terri Schiavo—a tragedy compounded. N Engl J Med. 2005;352(16):1630–3.
45. Wijdicks EFM. Law and bioethics. In: The comatose patient. New York: Oxford University Press; 2008. p. 201–16.
46. Jennett B. Ethical issues. In: The vegetative state: medical facts, ethical and legal dilemmas. Cambridge: Cambridge University Press; 2002. p. 97–125.
47. Racine E, Amaram R, Seidler M, Karczewska M, Illes J. Media coverage of the persistent vegetative state and end-of-life-decision-making. Neurology. 2008;71(13):1027–32.
48. Nizzi M-C, Demertzi A, Gosseries O, Bruno M-A, Jouen F, Laureys S. From armchair to wheelchair: how patients with a locked-in syndrome integrate bodily changes in experienced identity. Conscious Cogn. 2012;21(1):431–7.
49. Bruno M-A, Bernheim JL, Ledoux D, Pellas F, Demertzi A, Laureys S. A survey on self-assessed well-being in a cohort of chronic locked-in syndrome patients: happy majority, miserable minority. BMJ Open. 2011;1(1):e000039.
50. Demertzi A, Jox RJ, Racine E, Laureys S. A European survey on attitudes towards pain and end-of-life issues in locked-in syndrome. Brain Inj. 2014;28(9):1209–15.
51. Demertzi A, Laureys S. Detecting levels of consciousness. In: Clausen J, Levy N, editors. Handbook of neuroethics. Dordrecht: Springer; 2015. p. 665–77.

Chapter 14
Near-Death Experiences: Actual Considerations

Vanessa Charland-Verville, Charlotte Martial, Helena Cassol, and Steven Laureys

Abstract The notion that death represents a passing to an afterlife, where we are reunited with loved ones and live eternally in a utopian paradise, is common in the anecdotal reports of people who have encountered a "near-death experience" (NDE). These experiences are usually portrayed as being extremely pleasant including features such as a feeling of peacefulness, the vision of a dark tunnel leading to a brilliant light, the sensation of leaving the body, or the experience of a life review. NDEs are increasingly being reported as a clearly identifiable physiological and psychological reality of clinical and scientific significance. The definition and causes of the phenomenon as well as the identification of NDE experiencers are still matters of debate. The phenomenon has been thoroughly portrayed by the media, but the science of NDEs is rather recent and still lacking of rigorous experimental data and reproducible controlled experiments. It seems that the most appropriate theories to explain the phenomenon tend to integrate both psychological and neurobiological mechanisms. The paradoxical dissociation between the richness and intensity of the memory, probably occurring during a moment of brain dysfunction, offers a unique opportunity to better understand the neural correlates of consciousness. In this chapter, we will attempt to describe NDEs and the methods to identify them. We will also briefly discuss the NDE experiencers' characteristics. We will then address the main current explicative models and the science of NDEs.

V. Charland-Verville, Ph.D. (✉) • C. Martial • H. Cassol • S. Laureys
Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium
e-mail: vanessa.charland-verville@ulg.ac.be; coma@chu.ulg.ac.be

C. Schnakers, S. Laureys (eds.), *Coma and Disorders of Consciousness*,
DOI 10.1007/978-3-319-55964-3_14

Description of the Phenomenon

After recovering from a coma caused by brain injury, patients can sometimes report vivid perceptions and memories that have occurred during their period on seemingly unconsciousness. Some of these memories have been popularized under the expression "near-death experiences" (NDEs) [1]. NDEs can be defined as a set of mental events including highly emotional, self-related, mystical, and spiritual aspects occurring in an altered state of consciousness classically occurring in the context of a life-threatening condition (e.g., cardiac arrest, trauma, perioperative complications, intracerebral hemorrhage, septic or anaphylactic shock, near-drowning or asphyxia, electrocution, attempted suicide) [1–3]. The NDE core features most commonly include ranked by frequency feelings of peacefulness/well-being, out-of-body experience (OBE), seeing a bright light, an altered time perception, and entering some other, unearthly environment [4]. Despite their circumstances of occurrence, NDEs are generally experienced as extremely pleasant and can induce life-changing consequences on the experiencers' set of values and attitudes toward death [3]. However, in addition to the ill-described relation between the NDEs and the precipitating factors, the reliability of NDE accounts remains controversial.

Without being designated as such, NDEs were already addressed in Plato's Republic [5] and represented in paintings by Hieronymus Bosch during the fifteenth century (Fig. 14.1). The expression was unofficially first formulated in the nineteenth century when Albert von St. Gallen Heim, a Swiss geologist and alpinist, collected "near-death" testimonies from his fellow climbers and himself after climbing accidents in the Alps [8]. He described these experiences as being similar in their content including an expanded time perception, the review of past episodes of one's life, auditory perceptions containing music and various sounds, visions of idyllic landscapes, and the absence of pain at the moment of impact. Following Heim's work, the equivalent French term *Expérience de Mort Imminente* was proposed by the French psychologist and epistemologist Victor Egger. Some decades later, Moody [1] popularized the expression "near-death experience—NDE" through his best seller *Life After Life* in which he defined NDEs as "any conscious perceptual experience occurring in individuals pronounced clinically dead or who came very close to physical death." Moody drew a list of the most frequently recounted features by a recruited sample of 150 individuals coma survivors in intensive care who had been hospitalized after a near-fatal incident of various etiologies (Moody's features are described in Table 14.1). Later, NDEs have been defined as a "profound psychological event including transcendental and mystical elements, typically occurring to individuals close to death or in situations of intense physical or emotional danger" [2]. More such broad definitions of NDEs have been proposed like "transcendental experiences precipitated by a confrontation with death" [9] or "responses to life-threatening crisis characterized by a combination of dissociation from the physical body, euphoria, and transcendental or mystical elements" [10] and not all agree on the investigated phenomenology associated with a "typical" NDE rendering their scientific study difficult.

Fig. 14.1 Reproduction of Hieronymus Bosch's work "Ascent of the Blessed" (painted around 1490 in the Netherlands). Palazzo Ducale, Venice. "The image evokes a symbolic imagery, religious or esoteric, where after the end of earthly life, souls saved, helped by angels, throw off the last remains, and reborn in a different plane, rising almost without the support of its heavenly guides, following by a corridor (or tunnel) where an intense light emerges from the darkness and illuminates their path of ascension" [6]. Unfortunately, too little is known about the life of the painter to provide a satisfactory explanation of this work on the basis of his biographical background [7]. File taken from the Wikimedia Commons (http://en.wikipedia.org/wiki/File:Ascent_of_the_Blessed.jpg#globalusage)

Table 14.1 Common elements recurring in adult NDEs and their aftereffects [1]

Elements occurring during NDEs	Elements occurring as aftereffects
Ineffability	Frustration relating the experience to others
Hearing oneself pronounced dead	Subtle "broadening and deepening" of life
Feelings of peace and quiet	Elimination of fear of death
Hearing unusual noises	Corroboration of events witnessed while "out of the body"
Seeing a dark tunnel	
Being "out of the body"	
Meeting "spiritual beings"	
Experiencing a bright light as a "being of light"	
Panoramic life review	
Experiencing a realm in which all knowledge exists	
Experiencing cities of light	
Experiencing a realm of bewildered spirits	
Experiencing a "supernatural rescue"	
Sensing a border or limit	
Coming back "into the body"	

Identifying NDEs

According to a Gallup Poll, it was estimated that about 5% of the American population have had such an experience (or at least experienced some NDE features) in the context of a life-threatening situation [11]. More recently, surveys conducted in Australia [12] and Germany [13] have yield a prevalence of 4–15%. However, these values might not reflect the absolute frequency since many NDE experiencers can be uncomfortable of sharing their experience or might have forgotten about those memories [14]. Moreover, it is not clear how NDE experiencers are identified. To facilitate NDE identification, Ring [15] and Greyson [16] developed tools to use in clinical and research settings. Ring's "Weighted Core Experience Index (WCEI)" [15] was developed based on a previous narrative collection of 102 individuals who have been "close to death" from various contexts. The index aims at quantifying the depth of a NDE according to ten arbitrarily weighted items with a maximum score of 23 [15] (Table 14.2). According to Ring, if the individuals' scores are less than 6, they are not considered to have had "enough" of an experience to be qualified as a "core experiencer." Respondents scoring between 6 and 9 are considered as "moderate experiencers," and finally, those who score more than 10 will be qualified as "deep experiencers" [15]. Based on the narratives collected, he also proposed a

Table 14.2 Ring's Weighted Core Experience Index [15]

Components	Weight
Subjective sense of being dead	1
Feeling of peace, painlessness, pleasantness, etc.	2
Sense of bodily separation	2
Sense of entering a dark region	2
Encountering a presence/hearing a voice	3
Taking stock of one's life	3
Seeing, or being enveloped in, light	2
Seeing beautiful colors	1
Entering into the light	4
Encountering visible "spirits"	3

five-stage temporality sequence to describe NDEs: peace and contentment, detachment from physical body, entering a transitional region of darkness, seeing a brilliant light, and entering through the light into another realm of existence [15]. However, the actual sequence of NDE features remains an unexplored area.

Although useful in quantifying the depth of an experience, Ring's WCEI was neither based on statistical analyses nor tested for coherence or reliability. Ring's scale limitations were addressed with Greyson's construction of the "near-death experience scale—NDE scale" [16]. He began by selecting 80 features from the existing NDE literature and subsequently reduced these to a final validated [17] 16-item multiple-choice tool used to quantify the intensity of the NDE (i.e., total score ranging from 0 to 32) and to assess core content components of 16 NDE features (Table 14.3). For each item, the scores are arranged on an ordinal scale ranging from 0 to 2 (i.e., 0 = "not present," 1 = "mildly or ambiguously present," and 2 = "definitively present"; 16–17). The latter scale is also, according to its author, clinically useful in differentiating between individuals that have experienced NDEs and in excluding organic brain syndromes and nonspecific stress responses [16]. The scale is subdivided into four psychologically meaningful clusters: cognitive, affective, paranormal, and transcendental experiences. According to the scale, an individual with a NDE scale score of 7 or higher on the maximum of 32 qualifies as a NDE experiencer [16]. The Greyson NDE scale is the most widely used tool to standardize the identification of NDErs in research literature [18]. According to a recent retrospective collection of data obtained from 354 individuals with self-reported NDEs over a 7-year period using the NDE scale, the top three most reported features were (1) a feeling of peace or pleasantness (92%), (2) a feeling of detachment from the body (77%), and (3) seeing or feeling surrounded by a brilliant light (74%) [19].

Table 14.3 Greyson's NDE scale (1983)

Questions/features	Response
Cognitive	
1: Did time seem to speed up or slow down?	0 = No
	1 = Time seemed to go faster or slower than usual
	2 = Everything seemed to be happening at once; or time stopped or lost all meaning
2: Were your thoughts speeded up?	0 = No
	1 = Faster than usual
	2 = Incredibly faster
3: Did scenes from your past come back to you?	0 = No
	1 = I remembered many past events
	2 = My past flashed before me, out of my control
4: Did you suddenly seem to understand everything?	0 = No
	1 = Everything about myself or others
	2 = Everything about the universe
Affective	
*5: Did you have a feeling of peace or pleasantness?	0 = No
	1 = Relief or calmness
	2 = Incredible peace or pleasantness
6: Did you have a feeling of joy?	0 = No
	1 = Happiness
	2 = Incredible joy
7: Did you feel a sense of harmony or unity with the universe?	0 = No
	1 = I felt no longer in conflict with nature
	2 = I felt united or one with the world
*8: Did you see, or feel surrounded by, a brilliant light?	0 = No
	1 = An unusually bright light
	2 = A light clearly of mystical or other-worldly origin
Paranormal	
9: Were your senses more vivid than usual?	0 = No
	1 = More vivid than usual
	2 = Incredibly more vivid
10: Did you seem to be aware of things going on elsewhere, as if by extra sensorial perception/ telepathy?	0 = No
	1 = Yes, but the facts have not been checked out
	2 = Yes, and the facts have been checked out
11: Did scenes from the future come to you?	0 = No
	1 = Scenes from my personal future
	2 = Scenes from the world's future

Table 14.3 (continued)

Questions/features	Response
*12: Did you feel separated from your body?	0 = No
	1 = I lost awareness of my body
	2 = I clearly left my body and existed outside it
Transcendental	
13: Did you seem to enter some other, unearthly world?	0 = No
	1 = Some unfamiliar and strange place
	2 = A clearly mystical or unearthly realm
14: Did you seem to encounter a mystical being or presence or hear an unidentifiable voice?	0 = No
	1 = I heard a voice I could not identify
	2 = I encountered a definite being or a voice clearly of mystical or unearthly origin
15: Did you see deceased or religious spirits?	0 = No
	1 = I sensed their presence
	2 = I actually saw them
16: Did you come to a border or point of no return?	0 = No
	1 = I came to a definite conscious decision to "return" to life
	2 = I came to a barrier that I was not permitted to cross or was "sent back" against my will

*Top three most reported features of our recent study are marked with an asterisk (Charland-Verville et al. [4])

NDEs Not "Near Death"

Unlike these "classical" NDEs associated with impeding death or coma, "NDE-like" experiences have also been reported in situations where there was no genuine threat to the individuals' life. Only a few studies have assessed "NDE-like" phenomena in non-life-threatening situations [20–23]. Such accounts have also been reported in epileptic patients [24], syncope [25], intense grief and anxiety [26], Cotard's syndrome [27], and during meditative state [28]. These NDE-like experiences can be very strong and lead to profound life transformations just like "classical" NDEs. In a recent case study, the subject reported common NDE features in the context of grief after a divorce (e.g., the vision of a supernatural light, peacefulness, deep joy, and empathic fusion with the whole world) in the absence of critical cerebral or psychological disorders [20]. The subject reported no history of psychiatric disorders, use of psychotropic drugs, or substance abuse. It remains unclear whether some NDE features are exclusive to life-threatening or non-life-threatening situations and if they differ in intensity. It seems that NDE-like experiences are reported more frequently than usually assumed. Recent retrospective data highlighted that 21% of the self-reported NDEs occurred during a non-life-threatening context

(e.g., during sleep, after a concussion) [19] and that according to the Greyson NDE scale, no difference could be found in terms of intensity and reported content when comparing "classical NDEs" vs. NDE-like experiences [4]. Gabbard and Twemlow [22] have proposed that the expectancy of an incoming death or the strong belief of one's death would suffice to trigger NDEs.

Negative NDEs

Although NDEs are usually reported as being extremely pleasant, distressing or hellish experiences can also occur. Previous estimations suggest an incidence of 1–2% [4, 11, 29–31]. To document the frequency of frightening NDEs can be challenging because individuals might be reluctant to report them due to its post-traumatic stress component [32, 33]. Bush et al. [32] identified three types of frightening NDEs. First, the "inverse experience" has a similar content as a pleasant NDE (e.g., light, presences, knowledge, landscapes) but is perceived as an alien reality out of control and is extremely stressful. The second type involves perceptions of emptiness, the individual feels left alone, and nonexistent. The third type is the prototypical "hellish" encounter, with threatening entities, and various accouterments of the traditional hell, marked by perceptions of impending judgment and torment [32]. Whether the experience was perceived as being pleasant or frightening, some individuals have reported psychological distress related to the difficulty in integrating the experience and its consequences into their lives [34].

NDE Experiencers Characteristics

Previous work has aimed to investigate NDE experiencers' characteristics. So far, there is still no longitudinal study conducted, and the characteristics are assessed after the individual lived the experience. Therefore, in those who report a NDE, researchers aimed at (retrospectively) measuring personal characteristics that might be related to the NDE features reported and (prospectively) assessing the characteristics that might differentiate the individuals who report a NDE from those who don't [35]. According to age, studies performed among patients with cardiac arrest have shown that NDEs seem to be reported more frequently before the age of 60 [3, 14]. This tendency could be explained by the possibility of a greater vulnerability of older patients' brain to cerebral ischemia and more susceptible to amnesia. The same study highlighted the fact that having had a previous NDE could facilitate the reoccurrence of such an experience, as individuals can report multiple NDEs [3]. Using Ring's WCEI, van Lommel et al. [3] observed deeper NDEs in women, but no other studies reported such a difference in gender. This gender observation might

be partly explained by the fact that women might be less afraid to report a NDE [1] or that women have been found to score generally higher on anomalous-perception questionnaires than male subjects [36]. More demographic variables such as ethnicity, social class, religiosity, educational level, and factors like prior psychiatric disorders or psychiatric characteristics, suicidal behavior, or family history of suicidal have not been shown to influence the frequency of reported NDEs [3, 15, 37–40]. Most of the NDE literature comes from Western cultures, but according to the published data, taking into account religiosity and cultural background, these variables seem to have an influence on the NDEs' content and the features' interpretation [38, 41] (see Table 14.4 for an overview of non-Western NDE features). While Western experiencers might describe the presence perceived in their NDE as guardian angels, Hindus might see them as messengers of the god of death [42, 43]. Some authors have argued that NDEs would be culturally determined phenomena reflecting cultural and social influences [41]. In fact, it appears that some NDE features may not be universal like the tunnel vision [43]. The tunnel feature has been identified as a "cultural contaminant not necessarily integral to NDEs" [44]. In fact, when investigating NDE testimonials before and after Moody's best seller release in 1975, the only feature has been absent before 1975 was the tunnel vision. The authors explained that by suggesting that the societal models might have influenced this feature [44]. Even though the sociocultural background might influence the reported content and interpretation, the overall reports show sufficient common content and meaning to be considered a universal human experience of great interest for modern neuroscience [41, 45].

Table 14.4 Descriptive overview of five NDE features according to retrospective cases reported anecdotally around in non-Western countries (adapted from Greyson et al. 2000a)

Countries/continents	*N* of published cases	NDE features				
		Tunnel	OBE	Life review	Encounters with beings	Other world
China	180	±	+	+	+	+
India	109	−	+	+	+	+
Thailand	10	±	+	+	+	+
Tibet	16	−	+	+	+	+
Hawaii	1	±	+	−	+	+
Guam	4	−	+	−	+	+
New Zealand	1	±	+	−	+	+
South America	14	−	+	−	+	+
Australia	1	−	−	−	+	+
Africa	15	±	−	−	+	+

Note that similar features seem to be experienced worldwide
Most of the represented data are still anecdotal since NDEs were not identified through a standardized manner and the full narratives are not available. *OBE* out-of-body experience. China [99]; India [100]; Thailand [101]; Tibet [102]; Hawaii [103]; Guam [104]; New Zealand [105]; South America [106]; Australia [107]; Africa [108]. Symbols "+" and "−" used by the different authors to report the presence (+) or absence (−) of the feature

Research on NDEs

So far, the majority of published work on NDEs is retrospective and sporadic. NDEs are challenging to study as their occurrence is unpredictable, and they are generally not reported at their moment of occurrence, but days, months, or even only years later. The work of Moody [1] opened the way for scientific research on NDEs starting with the establishment in 1981 of the International Association for Near-Death Studies (IANDS) in the USA. The majority of the NDE studies aimed at identifying the presence of NDEs among various populations. Empirical studies on NDEs can be differentiated between retrospective and prospective designs (for a review of the main retrospective and prospective studies, see Table 14.5).

Retrospective research involves a convenient sample of individuals with so-called self-reported NDEs that have responded to the researchers' strategies of recruitment to share their NDE account. This research design dominates the field of NDE research and has been conducted among various populations: after a coma of different etiologies [4, 23, 46], cardiac arrest [14], suicide attempts [47], and uremic coma before dialysis therapy [48]. The main advantages of retrospective studies are that NDEs in various populations and from different contexts can be studied and that larger samples of experiences can be included. On the other hand, retrospective samples are always biased and include only NDEs of self-reporters, whom might share different accounts from individuals more reluctant to share their experience. Moreover, retrospectives NDEs are sometimes shared many years after they originally took place leading to a possible exaggeration the experience's content and intensity [49].

The prospective design usually follows a population of patients that are susceptible of experiencing a NDE in the context of a life-threatening medical condition. That way, researchers have access to complete medical information before and during the supposed occurrence of the NDE. In addition, NDE accounts are collected just a few days after the recovery. The prospective design reveals itself to be more rigorous than the retrospective one. However, prospective studies are expensive, heavy to set up, and only permit to recruit a narrower sample [35]. The prospective design have mostly been conducted among resuscitated patients after a cardiac arrest [3, 14, 39, 50–52] and (albeit more rarely) in patients with severe traumatic brain injury [53]. According to the NDE scale, 2–13% of the resuscitated patients after a cardiac arrest report accounts that are compatible with a NDE when asked an open question regarding any memories that could have occurred during the period surrounding their cardiac arrest and period of unconsciousness [51, 52]. Cardiac arrest survivors with NDEs cannot be distinguished by administered medications, metabolic states, psychology, sociodemographic factors, resuscitative interventions, or the duration of cardiac arrest or unconsciousness [3, 52, 54].

The choice of the study design can certainly have an impact on the collected data. It has been observed that fewer cases of NDEs are recounted by individuals interviewed prospectively than when the interviews are retrospectively conducted among self-reported NDE experiencers [49]. On the other hand, Greyson [109] argues that

Table 14.5 Overview of main NDE publications since Moody's popularization of the phenomenon

References	Type of material Title of book/ journal	Peer reviewed Medline/ PubMed	Study design Time since NDE	*N* Characteristics of the sample and inclusion criteria	NDEs (%)	Scale used to identify NDE minimum score	Reported features
Moody [1]	Book *Life After Life*	No	Retrospective NM	150 Individuals who reported an "unusual experience" after a coma of different etiologies	150	None	Please refer to Table 1 in the introduction section
Ring [15]	Book *Life at Death: A Scientific Investigation of the Near-Death Experience*	No	Retrospective NM	102 Self-reported NDEs of individuals claiming to have been "close to death"	49 (48)	The author introduces his scale—the WCEI and his five stages	Please refer to Table 2 in the introduction section
Sabom [31]	Book *Recollections of Death: A Medical Investigation*	No	Retrospective NM	111 Self-reported NDEs of individuals claiming to have been "close to death" with a majority of cardiac arrest survivors	47 (42)	None	NM

(continued)

Table 14.5 (continued)

References	Type of material Title of book/ journal	Peer reviewed Medline/ PubMed	Study design Time since NDE	*N* Characteristics of the sample and inclusion criteria	NDEs (%)	Scale used to identify NDE minimum score	Reported features
Gabbard and Twemlow [21]	Journal article *Omega: Journal of Death and Dying*	Yes Yes	Retrospective NM	339 Individuals with self-reported OBEs after life-threatening and non-life-threatening situations	34 (5)	None	NM
Ring and Franklin [110]	Journal article *Omega: Journal of Death and Dying*	Yes No	Retrospective NM	36 Suicide survivors of various etiologies	17 (47)	WCEI	NM
Sabom [31]	Book *Recollections of Death: A Medical Investigation*	No	Retrospective NM	116 Self-reported NDEs of individuals claiming to have been "close to death"	33 (28)	None	NM

Gallup and Proctor [11]	Book *Adventures in Immortality: A Look Beyond the Threshold of Death*	No	Retrospective NM	1500 Individuals from the general adult American population claiming to have been "close to death"	60 (4)	None	NM
Greyson [16]	Journal article *The Journal of Nervous and Mental Disease*	Yes Yes	Retrospective 18 ± 16 years	74 Self-reported NDEs of individuals claiming to have been "close to death"	62 (84)	The author introduces his scale—the Greyson NDE scale	Please refer to Table 3 in the introduction section
Greyson [47]	Journal article *Journal of Near-Death Studies*	Yes No	Retrospective ~17 days	61 Suicide survivors of various etiologies ranging from minor to potentially lethal attempts Subjects need a score of ≥6 to be included	16 (26)	WCEI 6/30	NM

(continued)

Table 14.5 (continued)

References	Type of material Title of book/ journal	Peer reviewed Medline/ PubMed	Study design Time since NDE	*N* Characteristics of the sample and inclusion criteria	NDEs (%)	Scale used to identify NDE minimum score	Reported features
Greyson [46]	Journal article *Journal of Near-Death Studies*	Yes No	Retrospective ~18 years	183 Self-reported NDEs of individuals claiming to have been "close to death" Subjects need a score of ≥7 to be included	183	Greyson NDE scale 7/32	The most reported features were the feeling of peacefulness (92%) as well as OBEs (86%). The least reported features were the life review (25%) and precognitive visions (14%)
Schoenbeck and Hocutt [111]	Journal article *Journal of Near-Death Studies*	Yes No	Prospective 5–52 days	11 Patients who have undergone cardiopulmonary resuscitation Subjects need a score of ≥7 to be included	1 (1)	Greyson NDE scale 7/32	The NDE was considered to be "transcendental" (encounter with a religious spirit; entering an unearthly world and coming to a boarder)

Zhi-ying and Jian-xun [112]	Journal article *Journal of Near-Death Studies*	Yes No	Retrospective 11 years	81 Survivors of the severe earthquake in Tangshan, China, in 1976 Subjects need a score of ≥7 to be included	32 (40)	Greyson NDE scale 7/32	Features' frequencies are measured among the whole sample ($N = 81$). The most reported features of experiencers and non-experiencers were the feeling of peacefulness (52%) as well as thought acceleration and life review (51%). The least reported features were the feeling of joy (10%) and precognitive visions (14%)
Orne [113]	Journal article *Research in Nursing and Health*	Yes No	Prospective 3–21 days	44 Cardiac arrest survivors Subjects need a score of ≥7 to be included	9 (20)	Greyson NDE scale 7/32	NM
Pacciolla [114]	Journal article *Journal of Near-Death Studies*	Yes No	Retrospective 3 months–10 years	64 Self-reported NDEs of individuals claiming to have been "close to death" Subjects need a score of ≥7 to be included	24 (38)	Greyson NDE scale 7/32	The most reported features were the feeling of peacefulness and the meeting with deceased or religious spirits (>75%), while the least reported features were the time distortion and the extrasensory perception (29%)

(continued)

Table 14.5 (continued)

References	Type of material Title of book/ journal	Peer reviewed Medline/ PubMed	Study design Time since NDE	*N* Characteristics of the sample and inclusion criteria	NDEs (%)	Scale used to identify NDE minimum score	Reported features
Knoblauch et al. [13]	Journal article *Journal of Near-Death Studies*	Yes No	Retrospective NM	2044 Individuals from the general adult German population Subjects need to report any Moody's features to be included	82 (4)	None	Open-ended questions lead to these main features (no ranking of frequency mentioned): transcendent reality, great feelings, contrast between light and dark, out-of-body experiences, panoramic memory or life review experiences, descriptions of landscapes
van Lommel et al. [3]	Journal article *The Lancet*	Yes Yes	Prospective 74% of the sample was interviewed 5 days after	344 Cardiac arrest survivors Subjects need to report any memory of the event to be included	62 (18%) with a minimum score of 141 (9%) with a minimum score of 6/30	WCEI scale 1/30	Positive emotions and the awareness of being dead were the most reported feature (56% and 50%), while the life review and the final boarder/point of no return were the least reported ones (13% and 8%)
Parnia et al. [52]	Journal article *Resuscitation*	Yes Yes	Prospective NM	63 Cardiac arrest survivors Subjects need a score of ≥7 to be included	4 (6)	Greyson NDE scale 7/32	All four patients in the NDE group sensed a final boarder/point of no return (100%), and three out of the four also experienced seeing a bright light and feelings of peace, pleasantness, and joy (75%)

Schwaninger et al. [39]	Journal article *Journal of Near-Death Studies*	Yes No	Prospective ~2–3 days after	30 Cardiac arrest survivors and coma survivors of various etiologies Subjects need a score of ≥7 to be included	7 (23)	Greyson NDE scale 7/32	The most reported features were the feeling of peacefulness (100%) and OBEs (90%), while the least reported ones were time distortion, thought acceleration, life review (9%), and extrasensory perception (0%)
Greyson [14]	Journal article *General Hospital Psychiatry*	Yes Yes	Prospective "Patients were approached as soon after admission as their condition had stabilized"	1595 Cardiac arrest survivors Subjects need a score of ≥7 to be included	27 (2)	Greyson NDE scale 7/32	The most reported feature was the feeling of peacefulness (85%), while the least reported one was precognitive visions (7%)
Greyson [37]	Journal article *Psychiatric Services*	Yes Yes	Retrospective NM	832 Psychiatric patients claiming to have been "close to death" Subjects need a score of ≥7 to be included	61 (7)	Greyson NDE scale 7/32	NM

(continued)

Table 14.5 (continued)

References	Type of material Title of book/ journal	Peer reviewed Medline/ PubMed	Study design Time since NDE	*N* Characteristics of the sample and inclusion criteria	NDEs (%)	Scale used to identify NDE minimum score	Reported features
Nelson et al. [10]	Journal article *Neurology*	Yes Yes	Retrospective NM	446 Self-reported NDEs of individuals claiming to have been "close to death" Subjects need a score of ≥7 to be included	55 (12)	Greyson NDE scale 7/32	NM
Lai et al. [48]	Journal article *American Journal of Kidney Diseases*	Yes Yes	Retrospective 7 ± 13 years	710 Dialysis patients who have had a previous close brush with death Some patients had more than one NDE/event Subjects need a score of ≥7 to be included	45 with 51 events (6)	Greyson NDE scale 7/32 WCEI 1/30	The most reported feature were the feeling of peacefulness (75%) and OBEs (73%), while the least reported features were the awareness of being dead, precognitive visions, and tunnel vision (<10%). The frequencies are based on the number of NDEs (n = 51)

Klemenc-Ketis et al. [51]	Journal article *Critical Care*	Yes Yes	Prospective NM	52 Out-of-hospital cardiac arrest survivors Subjects need a score of ≥7 to be included	11 (21)	Greyson NDE scale 7/32	NM
Corazza and Schifano [115]	Journal article *Substance Use & Misuse*	Yes Yes	Retrospective 1 month in 30% of the sample	125 Previous ketamine misusers recollecting a ketamine-related NDE Subjects need a score of ≥7 to be included	50 (40)	Greyson NDE scale 7/32	The most reported features were an altered time perception (90%) and OBE (88%), while the least reported ones were the meeting with deceased or religious spirits (14%) and the final boarder/point of no return (8%)
Hou et al. [53]	Journal article *Annals of Indian Academy of Neurology*	Yes Yes	Prospective >14 days after recovering consciousness	86 Post-traumatic coma Subjects need a score of ≥7 to be included	3 (4)	Greyson NDE scale 7/32	Semi-structured oral interviews lead to these main features: unique light visions, intense feelings of astonishment, pleasure and fear, sense of helplessness, "supernatural but logical experience," and changes in opinions about death

(continued)

Table 14.5 (continued)

References	Type of material Title of book/ journal	Peer reviewed Medline/ PubMed	Study design Time since NDE	*N* Characteristics of the sample and inclusion criteria	NDEs (%)	Scale used to identify NDE minimum score	Reported features
Charland-Verville et al. [4]	Journal article *Frontiers in Human Neuroscience*	Yes Yes	Retrospective 25 ± 17 years	190 Self-reported NDEs of coma survivors of various etiologies n = 140 and n = 50 after non-life-threatening situations Subjects need a score of ≥7 to be included	190	Greyson NDE scale 7/32	The most reported features for all groups were the feeling of peacefulness (89–93%) and OBEs (74–80%), while the least reported ones were the life review (18–37%) and precognition (17–20%)
Charland-Verville et al. [90]	Journal article *Consciousness and Cognition*	Yes Yes	Retrospective 19 ± 9 years	22 Patients with LIS and after a coma Subjects need a score of ≥7 to be included	8 (37)	Greyson NDE scale 7/32	The most reported features were: an altered time perception (75%), life review (75%), and OBEs (75%)

NDE near-death experience, *OBE* out-of-body experience, *NM* "not mentioned"; "close to death" and "various etiologies" situations can include: cardiac arrest, shock in postpartum, hemorrhage, perioperative complications, septic or anaphylactic shock, electrocution, coma resulting from traumatic brain damage, intracerebral hemorrhage or cerebral infarction, attempted suicide, near-drowning or asphyxia, and apnea

reports of NDEs are not modified over time, even 20 years after the original account. To the best of our knowledge, these results were not replicated, and no study has yet formally paid attention to the cognitive and phenomenological nature of such memories. In addition to the ill-described relation between the NDE and the precipitating factor, the reliability of NDE accounts remains controversial [55, 56].

Explicative Models for NDEs

Transcendental, psychological, and neurobiological theories have been proposed to account for the global phenomenon and more specifically for its core features.

Transcendental Theories

The scientific study of consciousness indicates that there is an intimate relationship between the mind and brain [57]. Interestingly, surveys conducted among highly educated medical professionals and scientists have revealed that "dualistic" attitudes toward the mind–brain relationship remain [58]. These are expressed through beliefs that the mind/soul is separable from the body or by the conviction that some spiritual part of us can survive after death [59]. Advocates of transcendental theories argue that postulating the NDEs represents a different state of consciousness (transcendence), in which the self, cognition, and emotions would function independently from the brain, but would retain the possibility of non-sensory perception, e.g., [60, 61]. To date, these theories lead the field of NDE research. Quantum physics models of nonlocal consciousness have also been used to support the premise of the continuation of mental function when the brain is apparently inactive or impaired or when an individual is "near death" [62, 63]. For these authors and others, the NDE phenomenon—especially the OBE core feature during which experiencers report having viewed their bodies from a different point in space and are able to describe accurately what was going on around them while they were considered unconscious—poses a serious challenge to current scientific understandings of the brain, mind, and consciousness [15, 31, 52]. However, protocols that have been set up to test for that hypothesis are still failing to confirm the veracity of such OBEs. For instance, a recent multicentric feasibility study had set up resuscitation and operating rooms with shelves containing targets (i.e., a combination of nationalistic and religious symbols, people, animals, and major newspaper headlines) that would be possible to see only from an elevated perspective usually described by the experiencers [116]. However, from the 2% of the patients' sample with explicit recall of "seeing" and "hearing" actual events related to their resuscitation, none of them could report seeing the targets. Like we will discuss in the next sections, neuroscientifically, it seems more probable that NDE features are the result of specific interactions between psychological and neurological mechanisms precipitated by the context of occurrence and an altered state of consciousness [18, 64].

Psychological Theories

The "awareness of being death" or very close to dying has been proposed to be an important factor for triggering NDEs. In fact, as suggested by Owens et al. [23], "it would seem that among individuals who were not near death their experiences could be precipitated by their belief that they were." The "expectation hypothesis" postulates that NDEs take their origin from an altered state of consciousness triggered by a life-threatening condition that could result in death without medical care. The NDE phenomenology would reflect the individual's system of beliefs and expectations of dying and a possible afterlife [23, 65, 66]. According to the "depersonalization and dissociation hypothesis," when facing a life-threatening situation, an individual would disconnect from the external world and engage in internally oriented fantasies as a projective defense mechanisms to make the new reality more intelligible and less distressing [67, 68]. Individuals with "fantasy-proneness personality" are described as having the propensity to focus their attention on imaginative or selected sensory experiences and to exclude other events from the external environment [69]. Finally, the NDE phenomenology has been proposed to be at least in part imagined mixing information available during the context of occurrence, the experiencers' prior knowledge, sociocultural background, fantasies or dreams, lucky guesses, and information from the remaining senses [70]. In fact, the brain is constantly trying to make sense of the information it receives. In order to preserve a coherent interpretation of highly stressful events associated with episodes of altered consciousness, NDEs could be built as a result of the individual's attempt to interpret its confusing experience [71] and the experiencers' the tendency to tell a good story. However, a recent study using the memory characteristic questionnaire [72] showed that when comparing the phenomenological content of NDE memories with imagined and real-life events memories, the NDEs are richer than both types of memories in terms of sensorial, emotional, contextual, and self-related characteristics [73]. Another hypothesis raises the possibility that at least some NDEs may be the result of false memories, with the mind trying to retrospectively "fill in the gap" after a period of unconsciousness [55].

Neurobiological Theories

These theories follow empirical findings on the brain mechanisms that are associated behaviorally and neuronally with NDEs. Recently, a study recorded electrophysiological state of rats' brain following cardiac arrest [74]. The brain is assumed to be hypoactive during cardiac arrest. However, results obtained by the researchers showed a transient and global surge of synchronized gamma oscillations, displaying high levels of interregional coherence and feedback connectivity. These results have led to the highly mediatized and criticized hypothesis that heightened conscious processing measured in rats after a cardiac arrest could serve as an explicative

model for the rich and realistic experiences associated with NDEs reported in the same context. Lempert et al. [25] while studying motor phenomena of vasovagal syncope incidentally observed that the faints were accompanied by memories. Sixty percent of the fainters reported vivid NDE-like features (e.g., feeling of peace, OBE, entering another world, life reviews). Syncopes were induced via the combination of hyperventilation and Valsalva maneuver (i.e., a forced expiration against the closed larynx) in healthy young adults [25, 75]. Harmless syncopes have since been proposed to be a good model to study NDEs [76]. Another theory has postulated that the transient impaired cerebral oxygen levels caused by a syncope (and more dramatically as in the context of a cardiac arrest) lead to a disruption of the physiological balance between conscious and unconscious states causing the ascending arousal system to blend rapid eye movement (REM) sleep attributed partly to the action of the locus coeruleus–noradrenergic system [10, 76]. The REM state can intrude into wakefulness as visual hallucinations, and during crisis, the atonia of REM intrusion could reinforce a person's sense of being dead and convey the impression of death to others. In line with that hypothesis, a cohort of NDE experiencers have been found to be more sensitive to REM sleep intrusions and sleep paralysis associated with hypnagogic and hypnopompic experiences [10]. It has also been suggested that NDEs would result from a massive release of endorphins in a condition of impeding death—at least for the positive feelings since the endorphins do not have hallucinatory properties [77]. Other authors have suggested that NDEs can be reported as hallucinatory experiences similar to what can be experienced with some drugs. Jansen et al. [78] have proposed the ketamine model for studying NDEs. This dissociative anesthetic and recreational drug has a blockade action on the glutamate N-methyl-D-aspartate (NMDA) receptors [79]. Likewise, conditions which can precipitate NDEs (e.g., decreased brain oxygen, blood flow, blood sugar) could increase the levels of glutamate release in the context of excitotoxic brain damage, stimulating the release of a ketamine-like neurotoxin [80, 81]. The phenomenology of a recreational ketamine experience have highlighted many similar features with NDEs: peace and tranquility, the conviction that one is dead, trips through dark tunnels into light, OBEs, seeing spirits, telepathic communion with God, and mystical states [82, 83].

The clinical core features of NDEs should provide an indication of their neurophysiologic basis. Altered blood gas levels (i.e., ischemia, hypoxia) has been suggested to induce NDE-like features. The mechanisms involved have been proposed to occur as a cascade of events, beginning by a neuronal disinhibition in early visual cortex spreading to other cortical areas [70, 84–86]. Blackmore [87] proposed that the tunnel vision and the perception of bright lights could be linked to the loss of bilateral peripheral visual field and retinal ischemia. Based on previous neuroimaging data, it seems clinically plausible that resuscitated patients with NDEs may suffer from transient ischemic and/or hypoxic lesions or interferences with bilateral occipital cortex and the optic radiation [23, 88, 89]. However, these speculations have to be regarded with caution; as to date, no neurological, neuropsychological, and neuroimaging data exist to corroborate these hypotheses empirically. As stated by Blackmore [70], the brain's altered oxygen levels are probably one of several related

mechanisms that lead to NDEs as it does not account for NDEs occurring in the absence of damage attributable to this mechanism.

In line with neurobiological theories, recent work aimed at assessing whether the etiology of the brain damage could influence the reported content and intensity [4]. The study could reveal that according to the Greyson NDE scale, the reported intensity and content of the NDE did not seem to vary across etiology groups. Another finding from this study, and in parallel from previous work [49], highlights that the study design (i.e., retrospective vs. prospective studies) seems to influence the reports of NDE, and in this case the content of what was reported (i.e., an altered time perception, the feeling of harmony and unity, the sudden understanding of everything, the heightened senses were more frequently reported retrospectively, while encounters with deceased or religious spirits were more frequently reported prospectively). In further work, authors assessed whether the brain lesion site would influence the reported Greyson NDE scale's features of a NDE. For this purpose, NDEs after a coma of patients with a locked-in syndrome (i.e., infratentorial brain stem lesions) and patients with supratentorial cortical lesions were compared. The results showed that the infratentorial lesions cohort reported less positive emotions and had a tendency to report more life review—in contradiction with the "classical" supratentorial cohort [90].

Studies with neurological patients have led to more hypotheses and findings about the neural correlates of NDE core features. For instance, it has been shown that the stimulation of the right temporoparietal junction area, including the anterior part of the angular gyrus and the posterior temporal gyrus, can produce OBEs caused by a deficient multisensory integration at the temporoparietal junction area. Focal electrical stimulation protocols in patients with epilepsy, migraine, or tinnitus have also been shown to induce repeated OBEs described from a visuospatial perspective localized outside the physical body and illusory transformations of the patient's limbs [91, 92]. Using a positron emission tomography (PET) scan, these authors also showed that the OBE was related to increased activity in the right superior temporal and precuneal cortices [92]. The out-of-body illusions may be the result of a complex illusory replication of one's body based on ambiguous input from proprioceptive, tactile, visual, and vestibular information and their integration at the disrupted temporoparietal junction area [93]. To some extent, these body illusions have also been reported in healthy individuals during microgravity conditions (inversion illusion during space mission or the low gravity phase of parabolic flights) [94], in the context of sleep paralysis [95] and virtual reality [96]. Behavioral findings have also included the left temporoparietal junction in a possible neural correlate of NDE features for the "feeling of a presence." Electrical stimulation of this brain area in a patient who was undergoing presurgical evaluation for epilepsy treatment provoked the strange sensation that somebody was nearby when no one was actually present [97]. In parallel to those findings, epileptiform activity was observed in the left temporal lobe in a population of NDE experiencers as compared to an age-matched population of individuals without NDEs [98].

In conclusion, there is currently no consensual or satisfying scientific explanation for NDEs. Although the phenomenon attracts a lot of attention from the media

worldwide, still just a handful of empirical studies are available. To date, transcendental interpretations have led the discussion of these empirical findings. These have largely omitted discussing of any psychological and neurobiological bases for these experiences and instead appear to prefer paranormal explanations over and above scientific enlightenment. The claims that NDEs are evidence for life after death may have contributed to the reluctance of designing rigorous empirical protocols to study such a "pseudoscience" phenomenon. In fact, the latest neurosciences evidence from consciousness research leads to the speculation that these experiences would rather emerge from a modified or altered brain functioning in an altered or modified state of consciousness resulting from various circumstances. We also hypothesize that all NDE features could be generated from specific neural correlates arranged in a biopsychosocial integrated phenomenon.

Acknowledgments The authors thank the IANDS Flanders and IANDS France (www.bijnadoodervaring.be; www.iands-france.org) for their collaboration in recruiting NDE testimonies. This research was supported by the Belgian National Funds for Scientific Research (FNRS) BIAL foundation, the European Commission (European ICT Programme Projects FP7-247919 DECODER), the Tinnitus Prize 2011 (FNRS 9.4501.12), the FEDER structural fund RADIOMED-930549, the Fonds Léon Fredericq, the James McDonnell Foundation, the French Speaking Community Concerted Research Action, and the University and University Hospital of Liège.

References

1. Moody RA. Life after life. New York: Bantam Press; 1975.
2. Greyson B. Near-death experiences. In: Cardena E, Lynn SJ, Krippner S, editors. *Varieties of anomalous experiences: examining the scientific evidence*. Washington: American Psychological Association; 2000a. p. 315–52.
3. van Lommel P, van Wees R, Meyers V, Elfferich I. Near-death experience in survivors of cardiac arrest: a prospective study in the Netherlands. Lancet. 2001;358(9298):2039–45.
4. Charland-Verville V, Jourdan JP, Thonnard M, Ledoux D, Donneau AF, Quertemont E, et al. Near-death experiences in non-life-threatening events and coma of different etiologies. Front Hum Neurosci. 2014;8:203.
5. Dent P. The Republic. London; 1937.
6. Hieronymus BW, Bosch C. 1450–1516: Between heaven and hell. Taschen; 2000. p. 104.
7. Engmann B. Near-death experiences: heavenly insight or human illusion? New York: Springer; 2014. p. 150.
8. Heim A. Notizen über den Tod durch Absturtz. Jahrbuch des Schweizer Alpenclub. 1891;21:327–37.
9. Irwin HJ, Watt CA. Near-death experiences. In: An introduction to parapsychology, 5th ed. McFarland; 2007.
10. Nelson KR, Mattingly M, Lee SA, Schmitt FA. Does the arousal system contribute to near death experience? Neurology. 2006;66(7):1003–9.
11. Gallup G, Proctor W. Adventures in immortality: a look beyond the threshold of death. New York: McGraw-Hill; 1982.
12. Perera M, Padmasekara G, Belanti J. Prevalence of near-death experiences in Australia. J Near Death Stud. 2005;24(2):109–15.
13. Knoblauch H, Schmied I, Schnettler B. Different kinds of near-death experience: a report on a survey of near-death experiences in Germany. J Near Death Stud. 2001;20:15–29.

14. Greyson B. Incidence and correlates of near-death experiences in a cardiac care unit. Gen Hosp Psychiatry. 2003;25(4):269–76.
15. Ring K. Life at death: a scientific investigation of the near-death experience. New York: Coward McCann & Geoghenan; 1980.
16. Greyson B. The near-death experience scale. Construction, reliability, and validity. J Nerv Ment Dis. 1983;171(6):369–75.
17. Lange R, Greyson B, Houran J. A Rasch scaling validation of a "core" near-death experience. Br J Psychol. 2004;95(2):161–77.
18. Vanhaudenhuyse A, Thonnard M, Laureys S. Towards a neuro-scientific explanation of near-death experiences? In: Yearbook of intensive care and emergency medicine. New York: Springer; 2009. p. 961–8.
19. Charland-Verville V, Martial C, Jourdan JP, Laureys S. A retrospective analysis of self-reported near-death experiences. Submitted. 2016.
20. Facco E, Agrillo C. Near-death-like experiences without life-threatening conditions or brain disorders: a hypothesis from a case report. Front Psych. 2012;3:490.
21. Gabbard GO, Twemlow SW, Jones FC. Do "near death experiences" occur only near death? J Nerv Ment Dis. 1981;169(6):374–7.
22. Gabbard G, Twemlow S. Do "near-death experiences" occur only near-death?—revisited. J Near Death Stud. 1991;10(1):41–7.
23. Owens JE, Cook EW, Stevenson I. Features of "near-death experience" in relation to whether or not patients were near death. Lancet. 1990;336(8724):1175–7.
24. Hoepner R, Labudda K, May TW, Schoendienst M, Woermann FG, Bien CG, et al. Ictal autoscopic phenomena and near death experiences: a study of five patients with ictal autoscopies. J Neurol. 2013;260(3):742–9.
25. Lempert T, Bauer M, Schmidt D. Syncope and near-death experience. Lancet. 1994;344(8925):829–30.
26. Kelly EW. Near-death experiences with reports of meeting deceased people. Death Stud. 2001;25(3):229–49.
27. McKay R, Cipolotti L. Attributional style in a case of Cotard delusion. Conscious Cogn. 2007;16(2):349–59.
28. Beauregard M, Courtemanche J, Paquette V. Brain activity in near-death experiencers during a meditative state. Resuscitation. 2009;80(9):1006–10.
29. Lindley JH, Bryan S, Conley B. Near-death experiences in a Pacific Northwest American population: the Evergreen study. Anabiosis. 1981;1:104–24.
30. Ring K. Heading toward omega: in search of the meaning of the near-death experience. New York: William Morrow; 1984.
31. Sabom M. Recollections of death: a medical investigation. New York: Harper & Row; 1982.
32. Bush NE. Afterward: making meaning after a frightening near-death experience. J Near Death Stud. 2002;21(2):99–133.
33. Greyson B, Bush NE. Distressing near-death experiences. Psychiatry. 1992;55:95–110.
34. Greyson B. The near-death experience as a focus of clinical attention. J Nerv Ment Dis. 1997;185(5):327–34.
35. Holden JM, Greyson B, James D. The handbook of near-death experiences. Praeger/ABC-CLIO: Santa Barbara; 2009.
36. Blanke O, Mohr C, Michel CM, Pascual-Leone A, Brugger P, Seeck M, et al. Linking out-of-body experience and self processing to mental own-body imagery at the temporoparietal junction. J Neurosci. 2005;25(3):550–7.
37. Greyson B. Near-death experiences in a psychiatric outpatient clinic population. Psychiatr Serv. 2003;54(12):1649–51.
38. Greyson B. Near-death experiences and spirituality. J Relig Sci. 2006;41(2):393–414.
39. Schwaninger J, Eisenberg PR, Schechtman KB, Weiss AN. A prospective analysis of near-death experiences in cardiac arrest patients. J Near Death Stud. 2002;20(4):215–32.
40. Wilson SC, Barber TX. The fantasy-prone personality: implications for understanding imagery, hypnosis, and parapsychological phenomena. PSI Res. 1982;1(3):94–116.

41. Belanti J, Perera M, Jagadheesan K. Phenomenology of near-death experiences: a cross-cultural perspective. Transcult Psychiatry. 2008;45(1):121–33.
42. Kellehear A. Census of non-western near-death experiences to 2005: observations and critical reflections. In: Holden JM, Greyson B, James D, editors. The handbook of near-death experiences: thirty years of investigations. Santa Barbara: Praeger/ABC-CLIO; 2009.
43. Pasricha S, Stevenson I. Near-death experiences in India. A preliminary report. J Nerv Ment Dis. 1986;174(3):165–70.
44. Athappilly GK, Greyson B, Stevenson I. Do prevailing societal models influence reports of near-death experiences?: a comparison of accounts reported before and after 1975. J Nerv Ment Dis. 2006;194(3):218–22.
45. Facco E, Agrillo C, Greyson B. Epistemological implications of near-death experiences and other non-ordinary mental expressions: moving beyond the concept of altered state of consciousness. Med Hypotheses. 2015;85(1):85–93.
46. Greyson B. Near-death encounters with and without near-death experiences: comparative NDE Scale profiles. J Near Death Stud. 1990;8:151–61.
47. Greyson B. Incidence of near-death experiences following attempted suicide. Suicide Life Threat Behav. 1986;16(1):40–5.
48. Lai CF, Kao TW, Wu MS, Chiang SS, Chang CH, Lu CS, et al. Impact of near-death experiences on dialysis patients: a multicenter collaborative study. Am J Kidney Dis. 2007;50(1):124–32. 132.e1–2
49. Mobbs D, Watt C. There is nothing paranormal about near-death experiences: how neuroscience can explain seeing bright lights, meeting the dead, or being convinced you are one of them. Trends Cogn Sci. 2011;15(10):447–9.
50. French CC. Near-death experiences in cardiac arrest survivors. In: Steven L, editor. Progress in brain research [Internet]. Elsevier; 2005. p. 351–67. http://www.sciencedirect.com/science/article/B7CV6-4H62GJY-13/2/709582cdef8e1a463779efddde61edf7
51. Klemenc-Ketis Z, Kersnik J, Grmec S. The effect of carbon dioxide on near-death experiences in out-of-hospital cardiac arrest survivors: a prospective observational study. Crit Care. 2010;14(2):R56.
52. Parnia S, Waller DG, Yeates R, Fenwick P. A qualitative and quantitative study of the incidence, features and aetiology of near death experiences in cardiac arrest survivors. Resuscitation. 2001;48(2):149–56.
53. Hou Y, Huang Q, Prakash R, Chaudhury S. Infrequent near death experiences in severe brain injury survivors—a quantitative and qualitative study. Ann Indian Acad Neurol. 2013;16(1):75–81.
54. AAN. Practice parameters for determining brain death in adults (summary statement). The quality standards subcommittee of the American Academy of Neurology. Neurology. 1995;45(5):1012–4.
55. French CC. Dying to know the truth: visions of a dying brain, or false memories? Lancet. 2001;358(9298):2010–1.
56. Martens PR. Near-death-experiences in out-of-hospital cardiac arrest survivors. Meaningful phenomena or just fantasy of death? Resuscitation. 1994;27(2):171–5.
57. Laureys S, Gosseries O, Tononi G. The neurology of consciousness: cognitive neuroscience and neuropathology. Oxford: Academic; 2015.
58. Zeman A. What in the world is consciousness? In: Steven L, editor. Progress in brain research [Internet]. Elsevier; 2005. p. 1–10. http://www.sciencedirect.com/science/article/pii/S0079612305500013
59. Demertzi A, Liew C, Ledoux D, Bruno M-A, Sharpe M, Laureys S, et al. Dualism persists in the science of mind. Ann N Y Acad Sci. 2009;1157(1):1–9.
60. Parnia S. Do reports of consciousness during cardiac arrest hold the key to discovering the nature of consciousness? Med Hypotheses. 2007;69(4):933–7.
61. van Lommel P. About the continuity of our consciousness. Adv Exp Med Biol. 2004;550:115–32.

62. Greyson B. Implications of near-death experiences for a postmaterialist psychology. Psychol Relig Spiritual. 2010;2(1):37.
63. Schwartz JM, Stapp HP, Beauregard M. Quantum physics in neuroscience and psychology: a neurophysical model of mind–brain interaction. Philos Trans R Soc Lond Ser B Biol Sci. 2005;360(1458):1309–27.
64. Blanke O, Dieguez S. Leaving body and life behind: out-of-body and near-death experience. In: Laureys S, Tononi G, editors. The neurology of consciousness. London: Academic; 2009. p. 303–25.
65. Appelby L. Near-death experience: analogous to other stress induced physiological phenomena. Br Med J. 1989;298:976–7.
66. Blackmore S, Troscianko T. The physiology of the tunnel. J Near Death Stud. 1988;8:15–28.
67. Greyson B. Dissociation in people who have near-death experiences: out of their bodies or out of their minds? The Lancet. 2000b;355(9202):460–3.
68. Noyes R, Slymen D. The subjective response to life-threatening danger. Omega. 1979;9:313–21.
69. Ring K, Rosing CJ. The omega project: an empirical study of the NDE-prone personality. J Near Death Stud. 1990;8(4):211–39.
70. Blackmore S. Dying to live: science and near-death experience. London: Grafton; 1993.
71. Braithwaite JJ. Towards a cognitive neuroscience of the dying brain. Skeptic. 2008;21:8–16.
72. Johnson MK, Foley MA, Suengas AG, Raye CL. Phenomenal characteristics of memories for perceived and imagined autobiographical events. J Exp Psychol Gen. 1988;117(4):371–6.
73. Thonnard M, Charland-Verville V, Brédart S, Dehon H, Ledoux D, Laureys S, et al. Characteristics of near-death experiences memories as compared to real and imagined events memories. PLoS One. 2013;8(3):e57620.
74. Borjigin J, Lee U, Liu T, Pal D, Huff S, Klarr D, et al. Surge of neurophysiological coherence and connectivity in the dying brain. Proc Natl Acad Sci U S A. 2013;110(35):14432–7.
75. Lempert T, Bauer M, Schmidt D. Syncope: a videometric analysis of 56 episodes of transient cerebral hypoxia. Ann Neurol. 1994;36(2):233–7.
76. Nelson KR. Near-death experience: arising from the borderlands of consciousness in crisis. Ann N Y Acad Sci. 2014;1330(1):111–9.
77. Carr DB. Endorphins at the approach of death. Lancet. 1981;1(8216):390.
78. Jansen KL. The ketamine model of the near-death experience: a central role for the N-methyl-D-aspartate receptor. J Near Death Stud. 1997;16:79–95.
79. Curran HV, Morgan C. Cognitive, dissociative and psychotogenic effects of ketamine in recreational users on the night of drug use and 3 days later. Addiction. 2000;95(4):575–90.
80. Jansen K. Near death experience and the NMDA receptor. Br Med J. 1989;298(6689):1708.
81. Jansen KL. Using ketamine to induce the near-death experience: mechanism of action and therapeutic potential. Yearbook for Ethnomedicine and the Study of Consciousness. 1996;(4):51–81.
82. Collier BB. Ketamine and the conscious mind. Anaesthesia. 1972;27(2):120–34.
83. Coyle JT, Basu A, Benneyworth M, Balu D, Konopaske G. Glutamatergic synaptic dysregulation in schizophrenia: therapeutic implications. In: Novel antischizophrenia treatments. Berlin: Springer; 2012. p. 267–95.
84. Rodin EA. The reality of death experiences. A personal perspective. J Nerv Ment Dis. 1980;168(5):259–63.
85. Saavedra-Aguilar DJC, Gómez-Jeria LJS. A neurobiological model for near-death experiences. J Near Death Stud. 1989;7(4):205–22.
86. Woerlee GM. Mortal minds: the biology of near-death experiences. Amherst, NY: Prometheus Books; 2005.
87. Blackmore S. Near-death experiences. J R Soc Med. 1996;89(2):73–6.
88. Ammermann H, Kassubek J, Lotze M, Gut E, Kaps M, Schmidt J, et al. MRI brain lesion patterns in patients in anoxia-induced vegetative state. J Neurol Sci. 2007;260(1–2):65–70.

89. Els T, Kassubek J, Kubalek R, Klisch J. Diffusion-weighted MRI during early global cerebral hypoxia: a predictor for clinical outcome? Acta Neurol Scand. 2004;110(6):361–7.
90. Charland-Verville V, Lugo Z, Jourdan J-P, Donneau A-F, Laureys S. Near-death experiences in patients with locked-in syndrome: not always a blissful journey. Conscious Cogn. 2015;34:28–32.
91. Blanke O, Ortigue S, Landis T, Seeck M. Stimulating illusory own-body perceptions. Nature. 2002;419(6904):269–70.
92. De Ridder D, Van Laere K, Dupont P, Menovsky T, Van de Heyning P. Visualizing out-of-body experience in the brain. N Engl J Med. 2007;357(18):1829–33.
93. Blanke O, Landis T, Spinelli L, Seeck M. Out-of-body experience and autoscopy of neurological origin. Brain. 2004;127(Pt 2):243–58.
94. Lackner JR. Sense of body position in parabolic flight. Ann N Y Acad Sci. 1992;656:329–39.
95. Cheyne JA, Girard TA. The body unbound: vestibular-motor hallucinations and out-of-body experiences. Cortex. 2009;45(2):201–15.
96. Maselli A, Slater M. Sliding perspectives: dissociating ownership from self-location during full body illusions in virtual reality. Front Hum Neurosci. 2014;8:693.
97. Arzy S, Seeck M, Ortigue S, Spinelli L, Blanke O. Induction of an illusory shadow person. Nature. 2006;443(7109):287–7.
98. Britton WB, Bootzin RR. Near-death experiences and the temporal lobe. Psychol Sci. 2004;15(4):254–8.
99. Becker C. The centrality of near-death experiences in Chinese Pure Land Buddhism. Anabiosis. 1981;4:51–68.
100. Kellehear A, Stevenson I, Pasricha S, Cook EW. The absence of tunnel sensations in near-death experiences from India. J Near Death Stud. 1994;13:109–13.
101. Murphy T. Near-death experiences in Thailand. J Near Death Stud. 2001;19(3):161–78.
102. Bailey LW. A "little death": the near-death experience and Tibetan Delogs. J Near Death Stud. 2001;19(3):139–59.
103. Kellehear A. An Hawaiian near-death experience. J Near Death Stud. 2001;20(1):31–5.
104. Green JT. Near-death experiences in a Chamorro culture. Vital Signs. 1984;4(1–2):6–7.
105. King M. Being Pākehā: an encounter with New Zealand and the Māori renaissance. Auckland: Hodder and Stoughton; 1985.
106. Gómez-Jeria JS. A near-death experience among the Mapuche people. J Near Death Stud. 1993;11(4):219–22.
107. Berndt RM, Berndt CH. The speaking land: myth and story in aboriginal Australia. Harmondsworth: Penguin; 1989.
108. Morse M, Perry P. Closer to the light. New York: Villiard Books. 1990.
109. Greyson B. Consistency of near-death experience accounts over two decades: are reports embellished over time? Resuscitation, 2007;73(3):407–411.
110. Ring K, Franklin S. Do suicide survivors report near-death experiences?. OMEGA-Journal of Death and Dying, 1982;12(3):191–208.
111. Schoenbeck SB, Hocutt GD. Near-death experiences in patients undergoing cardiopulmonary resuscitation. Journal of Near-Death Studies. 1991;9(4):211–218.
112. Zhi-ying F, Jian-xun L. Near-death experiences among survivors of the 1976 Tangshan earthquake. Journal of Near-Death Studies. 1992;11(1):39–48.
113. Orne RM. The meaning of survival: The early aftermath of a near-death experience. Research in nursing & health. 1995;18(3):239–247.
114. Pacciolla A. The near-death experience: A study of its validity. Journal of Near Death Studies. 1996;14:179–186.
115. Corazza O, Schifano F. Near-death states reported in a sample of 50 misusers. Substance use & misuse. 2010;45(6):916–924.
116. Parnia S, Spearpoint K, de Vos G, Fenwick P, Goldberg D, Yang J, Wood M. AWARE—AWAreness during REsuscitation—A prospective study. Resuscitation. 2014;85(12): 1799–1805.

Chapter 15
Future Perspectives of Clinical Coma Science

Steven Laureys and Caroline Schnakers

Abstract As illustrated in the previous chapters, the clinical management of disorders of consciousness remains very difficult, but technological advances in neuroimaging, in EEG-based brain–computer interfaces, and in treatments are now offering new ways to improve the diagnostic, prognostic, and therapeutic management of these challenging conditions. In this chapter, we will discuss the recent international clinical research efforts in this challenging field, heralding a new era of consciousness science and coma management.

In the Past…

Historically, the seat of consciousness was widely believed to be in the heart, and the absence of heartbeat was regarded as the clinical sign of death. Neurological scientific evidence has superseded such thinking and shown that consciousness, an emergent property of neural activity, resides in the brain [1]. Since the invention of the positive-pressure mechanical respirator, it has become possible to truly dissociate cardiac, respiratory, and brain functions in individuals who are in a coma. Patients who would previously have died from apnea are now able to survive in profound comatose states that had never been encountered before. This technological progress forced modern medicine to redefine the diagnosis of death and move from its ancient cardiorespiratory-centered definition to a neurocentric one, where death is defined as the irreversible loss of all brainstem reflexes (including the

S. Laureys, M.D., Ph.D.
Coma Science Group, GIGA Research Center and Neurology Department, University and University Hospital of Liège, Liège, Belgium
e-mail: steven.laureys@ulg.ac.be

C. Schnakers, Ph.D. (✉)
Department of Neurosurgery, University of California Los Angeles, Los Angeles, CA, USA

Department of Research, Casa Colina Hospital and Centers for Healthcare, Pomona, CA, USA
e-mail: cschnakers@ucla.edu; cschnakers@casacolina.org

C. Schnakers, S. Laureys (eds.), *Coma and Disorders of Consciousness*,
DOI 10.1007/978-3-319-55964-3_15

breathing reflex). Since the introduction of this clinical definition, not a single patient who was declared brain dead has ever regained consciousness.

The origin of coma research, as a science, probably dates to 1966 when Fred Plum and Jerome Posner published the first edition of their classic text "The Diagnosis of Stupor and Coma" [2]. For the first time, researchers correlated clinical findings that were derived from the examination of patients in comatose states with pathological findings and proposed a pathophysiology of consciousness. In 1974, Bryan Jennett and colleagues published the Glasgow Coma Scale [3] and, in the next year, the Glasgow Outcome Scale [4]. These standardized scoring systems enabled the performance of multicenter clinical trials and epidemiological studies that resulted in the development of rational algorithms for the treatment (or withdrawal thereof) of comatose patients.

Pioneers such as Jennett and Plum revolutionized the field of acute brain injury. However, the excitement of the 1970s was followed by a return to therapeutic nihilism (i.e., the assumption that patients with chronic disorders of consciousness are uniformly hopeless cases) and a marked decrease of scientific interest in disorders of consciousness. Coma research nearly got comatose.

The emergence of functional neuroimaging techniques (such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI)) opened new opportunities to study brain activity in patients with DOC. The use of those techniques allowed to improved ability to delineate neural processes linked to consciousness. We know now that most patients in VS present with partial activation of sensory networks and impaired functional connectivity contrary to patients in MCS. Low-level primary cortical activity seems to be isolated from higher-level associative cortical activity, and recent findings suggest that long-distance connectivity (e.g., between frontal and temporal areas) is more impaired than short-distance connectivity (e.g., areas within the temporal gyrus) [5]. The reemergence of thalamocortical connections has also been associated with recovery of consciousness, whereas thalamic atrophy has been associated to chronic DOC [5, 6]. The brain activity in some patients with VS may nevertheless differ from findings suggesting altered brain activity. In 2006, Owen and colleagues reported the landmark case of a young woman who was clinically diagnosed as being in a VS. Yet, when performing a mental imagery task during an fMRI scan, her brain activity was similar to the pattern of activity observed in healthy controls [7]. Since then, other case studies have reported similar observations suggesting an underestimation of cognitive processing and the existence of a "covert cognition" in a minority of patients diagnosed as being in a VS.

Recent Findings on Assessment and Treatment

Thanks to all those findings, new techniques and paradigms aiming to improve the assessment and the treatment of patients with DOC started to emerge. With regard to assessment, Stender and colleagues have demonstrated, in a large sample, the

utility of PET scan when detecting conscious brain activity based on the preservation of frontoparietal networks. The technique allowed these researchers to correctly identify 93% of patients in MCS and to correctly predict consciousness recovery in 74% of patients with DOC [8].

Based on previous findings on functional connectivity, Casali and colleagues proposed the perturbational complexity index (PCI) as a measure of effective connectivity by calculating the spatial and temporal response of the brain to a perturbation induced by transcranial magnetic stimulation. The PCI distinguishes alert, healthy volunteers from volunteers who were anesthetized, sedated, and asleep and differentiated patients who were conscious (locked-in syndrome, MCS, and emerged from MCS) from those who were unconscious (VS) [9]. Finally, a series of fMRI and electroencephalography-based brain–computer interfaces are under development to detect "VS" patients with covert cognition [10]. Brain–computer interfaces are motor-independent systems that use brain activity to drive external devices or computer interfaces. These systems could represent a complementary tool for detecting command-following and for allowing complex ideas to be communicated to the outside world despite severe motor dysfunctions. The development of these interfaces is based on the idea that patients in VS who respond to active paradigms have preserved cognition. Such an idea has recently been challenged and should be further investigated [11].

With regard to treatment, Giacino, Whyte, and colleagues have recently demonstrated the efficacy of a pharmacological treatment with amantadine (a dopaminergic agent), which seems to modulate cortico-cortical (e.g., frontoparietal) network. In the context of this 11-site international, multicenter, randomized, and controlled trial, rate of recovery in both VS and MCS was significantly faster in the amantadine group as compared to those who received placebo [12]. There is also a growing interest in the use of invasive and noninvasive brain stimulation techniques to restore cortico-cortical but also thalamocortical connections in patients with prolonged DOC. The central premise used to guide these therapies is that electrical or magnetic stimulation elicits action potentials and depolarization of target neurons in cortical networks that underlie key functional systems (e.g., arousal, drive, language) responsible for behavioral initiation and control. Using a blinded alternating crossover design, Schiff, Giacino, and colleagues observed treatment-related behavioral improvements in a patient with TBI in MCS who was treated with deep brain stimulation of the thalamic intralaminar nuclei more than 6 years post-onset [13].

The use of noninvasive brain stimulation techniques such as transcranial direct current stimulation has also been investigated in the context of treatment of persons in DOC. Thibaut and colleagues administered this technique in 55 patients with DOC using a double-blind sham-controlled crossover design. In each patient, a single stimulation and sham session were applied over the left dorsolateral prefrontal cortex. Behavioral improvements have been observed in patients in MCS directly after the stimulation session, whereas such improvements were not observed after the sham session [14].

In the Future…

Even though it remains difficult to manage patients with severe brain injury, the field is in a rapid state of evolution. Ten years ago, everything was about characterizing and understanding consciousness processing. Clinicians would mainly collaborate with neuroscientists and help them to recruit to improve theoretical understanding, knowing it would not directly impact their practice. Now, the knowledge we have accumulated (and that we are still accumulating) is starting to have real translational ability to patient assessment and treatment. If this exponential increase of publication and interest continues, it will soon lead to even more substantial changes in the way we perceive the role of neurorehabilitation in those patients with DOC. In this context, recent initiatives have been created to develop international networks of collaboration. The American Congress of Rehabilitation Medicine and International Brain Injury Association have both recently created a special interest group with the mission to provide an international forum for exchange between brain injury professionals and neuroscientists on the study, assessment, and care of persons with disorders of consciousness, their families, and the systems serving them. This is truly an exciting time for the field, full of hope but also full of challenges. Assessment and treatment options need a lot more development and validation to be able to one day be implemented in clinical practice. In an experimental setting, the study of this population is also extremely challenging. These patients are sometimes difficult to recruit and retain, often easily exhausted and agitated, limiting the sample size, the assessment window, and the data quality. The development of a research environment adapted to the scientific investigation of these patients is time consuming and requests important clinical and scientific expertise. Coordinating multidisciplinary resources and knowledge (particularly between clinicians and neuroscientists) is therefore more than ever needed. Such collaboration will certainly help to overcome those complications and will lead, on the long term, to significant improvements in the care of patients with severe brain injury.

References

1. Demertzi A, Liew C, Ledoux D, et al. Dualism persists in the science of mind. Ann N Y Acad Sci. 2009;1157:1–9.
2. Posner J, Saper C, Schiff N, Plum F, editors. Diagnosis of stupor and coma. 4th ed. New York: Oxford University Press; 2007.
3. Jennett B, Plum F. Persistent vegetative state after brain damage: a syndrome in search of a name. Lancet. 1972;1:734–7.
4. Teasdale G, Jennett B. Assessment and prognosis of coma after head injury. Acta Neurochir. 1976;34(1–4):45–55.
5. Giacino JT, Fins JJ, Laureys S, Schiff ND. Disorders of consciousness after acquired brain injury: the state of the science. Nat Rev Neurol. 2014;10(2):99–114.

6. Lutkenhoff ES, McArthur DL, Hua X, et al. Thalamic atrophy in antero-medial and dorsal nuclei correlates with six-month outcome after severe brain injury. Neurol Clin. 2013;3: 396–404.
7. Owen AM, Coleman MR, Boly M, et al. Detecting awareness in the vegetative state. Science. 2006;313(5792):1402.
8. Stender J, Gosseries O, Bruno MA, et al. Diagnostic precision of PET imaging and functional MRI in disorders of consciousness: a clinical validation study. Lancet. 2014;384(9942): 514–22.
9. Casali AG, Gosseries O, Rosanova M, et al. A theoretically based index of consciousness independent of sensory processing and behavior. Sci Transl Med. 2013;5(198):198ra105.
10. Chatelle C, Chennu S, Noirhomme Q, et al. Brain-computer interfacing in disorders of consciousness. Brain Inj. 2012;26(12):1510–22.
11. Schnakers C, Giacino JT, Løvstad M, et al. Preserved covert cognition in noncommunicative patients with severe brain injury? Neurorehabil Neural Repair. 2015 May;29(4):308–17.
12. Giacino JT, Whyte J, Bagiella E, et al. Placebo-controlled trial of amantadine for severe traumatic brain injury. N Engl J Med. 2012;366(9):819–26.
13. Schiff ND, Giacino JT, Kalmar K, et al. Behavioural improvements with thalamic stimulation after severe traumatic brain injury. Nature. 2007;448(7153):600–3.
14. Thibaut A, Bruno MA, Ledoux D, et al. tDCS in patients with disorders of consciousness: Sham-controlled randomized double-blind study. Neurology. 2014;82(13):1112–8.

Index

C. Schnakers, S. Laureys (eds.), *Coma and Disorders of Consciousness*,
DOI 10.1007/978-3-319-55964-3