# Coma and Disorders of Consciousness

Caroline Schnakers
Steven Laureys
*Editors*

*Third Edition*

Springer

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*Editors*
Caroline Schnakers
Research Institute
Casa Colina Hospital and Centers for Healthcare
Pomona, CA, USA

Steven Laureys
Coma Science Group
GIGA-Consciousness
University of Liège
Liège, Belgium

CERVO Brain Research Center
Laval University
Québec, QC, Canada

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

# Foreword

It is with great pleasure that I write this foreword for the third edition *Coma and Disorders of Consciousness* edited by Caroline Schnakers and Steven Laureys. The third edition has been both revised and updated with the inclusion of some new areas of focus as well as new authors. The last edition of this important text on Disorders of Consciousness (DoC) was in 2018. In the last 5 years, we have certainly seen quite a burgeoning of research and expansion of our collective knowledge base regarding DoC that serves as fertile soil for this third edition. As our scientific evidence-base grows across different aspects of assessment and management of DoC, we will be better able to drive care based on science as opposed to historical dogma and/or practitioner experience.

Although DoC controversies still persist both neuroscientifically and neurorehabilitatively, this volume by Schnakers and Laureys addresses such a diversity of topics that anyone involved with interfacing at any level with this patient population should have this book on their shelf. Important topics that are covered include updates on neural correlates of consciousness, behavioral assessment including challenges of bedside assessment and neurologic recovery patterns, BCIs and their application to patients with DOC, as well as prognostication and long-term patterns of recovery as well as their medical, ethical, and legal implications. Neuromedical comorbidities across different states of disordered consciousness as well as management of same is an essential chapter relative to implications for decreasing morbidity and mortality in this patient population. The longstanding and controversial topic of sensory stimulation programs is addressed with an emphasis on newer data examining the potential efficacy of music therapy in this context. Chapters dealing specifically with treatment interventions involving pharmacotherapy as well as neuromodulation provide readers with up-to-date evidence-based information as well as theoretical posits of how such interventions may alter recovery of consciousness. Important chapters that are often not included in such texts cover topics on ethics, systems of care as well as caregiver burden/quality of life. Pediatric issues germane to diagnosis, prognosis, and treatment are also covered including the exploration of the gaps in this literature base. A very interesting chapter on near-death experiences examines psychological as well as neurobiological mechanisms of NDE and their implications for better understanding of the neural correlates of consciousness. The last chapter, authored by the editors, examines directions for the future driven by ongoing guideline development as well as advances in neuroimaging and EEG-based BCIs.

This volume will provide readers, whether physicians, other healthcare practitioners or other interested parties, with a critical informational foundation to truly gain an understanding of our current knowledge regarding disorders of consciousness. The information contained herein is quintessential to moving the field forward in improving the diagnosis, prognosis and treatment, both acute and long-term, of persons with DoC. The topics covered are diverse yet essential in garnering an appreciation for the complexities that we as clinicians face with this small albeit challenging patient population.

Department of Physical Medicine and Rehabilitation Nathan D. Zasler
Virginia Commonwealth University
Richmond, VA, USA

Concussion Care Centre of Virginia, Ltd.
Richmond, VA, USA

# 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 were 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.

While the management of patients with severe brain injury remains challenging, the field is rapidly evolving. Just a decade ago, the primary focus was on characterizing and comprehending consciousness processing. Clinicians predominantly collaborated with neuroscientists, helping them in recruitment to enhance theoretical understanding, even if its direct impact on practice was very limited. Currently, the amassed knowledge—continuously expanding—holds tangible potential for patient assessment and treatment. Should this exponential surge in publications and interest persist, substantial shifts in the perception of neurorehabilitation's role for patients with disorders of consciousness (DOC) are imminent.

In light of this, recent endeavors have arisen to foster global networks of collaboration. Guidelines containing research evidence on treatment and appropriate management of DoC have been published and are disseminated. Of course, conducting research within an experimental framework also presents considerable difficulties when dealing with this population. These patients are occasionally hard to enlist and maintain, often prone to fatigue and agitation. Thus, the existing coordination of multidisciplinary resources and knowledge—particularly between clinicians and neuroscientists—has become more crucial than ever before. Such collaboration undoubtedly holds the potential to surmount these complexities and is already now driving substantial enhancements in the care of patients with severe brain injuries.

This book is meant both for clinicians and researchers and contains a summary of recent findings on diagnostic/prognostic, assessment techniques (i.e., behavioral scales, multi-modal assessment and brain–computer interface), clinical management and experimental treatment (particularly, neuromodulation) which, we hope, will stimulate ideas for clinicians and 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.

Pomona, CA, USA Caroline Schnakers
Liege, Belgium Steven Laureys

# Contents

# Chapter 1
# Neural Correlates of Consciousness

**Benedetta Cecconi, Glenn van der Lande, and Arianna Sala**

**Abstract** Significant advances have been made in the behavioral assessment and clinical management of disorders of consciousness (DoC). In addition, functional neuroimaging paradigms are now available to help assess consciousness levels in this challenging patient population. The success of these neuroimaging approaches as diagnostic markers is, however, intrinsically linked to understanding the relationships between consciousness and the brain. In this context, we will review the neural correlates of consciousness through various altered states such anesthesia and sleep and review how these relate to pathologies such as DoC after a severe acquired brain injury.

## Introduction

Understanding the relationships between consciousness and the brain is a long-standing question of neuroscience, psychology, and philosophy [1]. In this chapter, we will provide an overview of the current state of research in this field, from the standpoint of neuroscience. Firstly, we will provide a definition of neural correlates of consciousness (NCC), distinguishing between content- and state-NCC, background conditions, and consequences of consciousness. Secondly, we will describe neurophysiological findings in physiological (sleep), pharmacological (anesthesia), and pathological (disorders of consciousness) states of consciousness. Finally, we will discuss challenges and future perspectives in integrating these findings to produce a definitive account on the NCC.

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B. Cecconi · G. van der Lande · A. Sala (✉)
Coma Science Group, GIGA-Consciousness, University of Liège, Liège, Belgium

Centre du Cerveau$^{(2)}$, University Hospital of Liège, Liège, Belgium
e-mail: benedetta.cecconi@uliege.be; glenn.vanderlande@uliege.be; arianna.sala@uliege.be

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## The Neural Correlates of Consciousness

From a philosophical perspective, consciousness has been defined as the phenomenological experience or the "what it is like" to perceive, feel, or think about a given object [2]. Investigating the variations in neural activity accompanying variations in conscious experience represents a common search strategy to identify the neural correlates of consciousness (NCC) [1]. More precisely, finding the NCC means identifying the "minimum neural mechanisms sufficient for any one specific conscious percept" [1] or identifying "a neural system whose state directly correlates with whether a subject is conscious or not" [2]. Building on these complementary definitions, a distinction has been proposed between the so-called content- and state-NCC [3].

The *content*-NCC are the neural mechanisms underlying a given "phenomenal distinction" in subjective experience, being specific to a given content of consciousness. The content-NCC are typically studied in experimental paradigms where the visibility of a target is systematically manipulated so that in some trials the subject is aware of the target and in others (s)he is not, while the general state of the subject is maintained unchanged (e.g., constantly awake, attentive); to distill the content-NCC, the neural activity when the target stimulus is perceived is compared to the neural activity when the target stimulus is not perceived [1].

The *state*-NCC are the neural mechanisms underlying global, non-specific states of consciousness (e.g., alert wakefulness, dreaming, anesthesia) that regulate the range of cognitive systems an individual can mobilize, and hence the range and quality of conscious contents an individual can experience while in that state [4]. The state-NCC are typically studied by comparing neural activity in a state of consciousness (e.g., alert wakefulness) with neural activity in a state of unconsciousness (e.g., coma). Alternatively, within-state paradigms can be used, where brain activity across fluctuations in consciousness is contrasted *within* the same physiological state, e.g., dreaming during Rapid Eye Movement (REM) sleep (denoting consciousness) vs dreamless REM sleep (unconsciousness) [1]. The latter approach has the advantage of removing physiological differences that might occur across different states of consciousness, which are nevertheless unrelated to consciousness, and that might confound the results [5].

A further distinction is made between NCC and their *background conditions* and *consequences*. The *background conditions* are defined as factors that enable consciousness but do not directly contribute to it, as is the case for the neural activating system that contributes to vigilance and attention by widespread modulation of cortical activity, but does not contribute directly to the conscious experience [5]. The *consequences* of consciousness are, for example, the ability to produce a verbal or otherwise behavioral report of the subject's own conscious experience. The background conditions and consequences of consciousness require particular attention as they might act as confounders in studies aiming at identifying the NCC. For example, when studying the NCC using task-based paradigms that require behavioral reporting on the subject's subjective experience, one should be careful in distinguishing between neural activity directly related to the conscious experience and neural activity related to the task of reporting [1].

In this chapter, we will focus on the state-NCC as identified via investigation of neural activity in different physiological, pharmacological, and pathological states of consciousness. These different states of consciousness are characterized by different levels of arousal (referring to the general state of wakefulness or alertness) and awareness (referring properly to the subjective experience) [6] (see Fig. 1.1). Brain activity is compared across or within different states of consciousness, using different neurophysiological techniques, to identify the patterns of brain activity that co-vary with awareness.

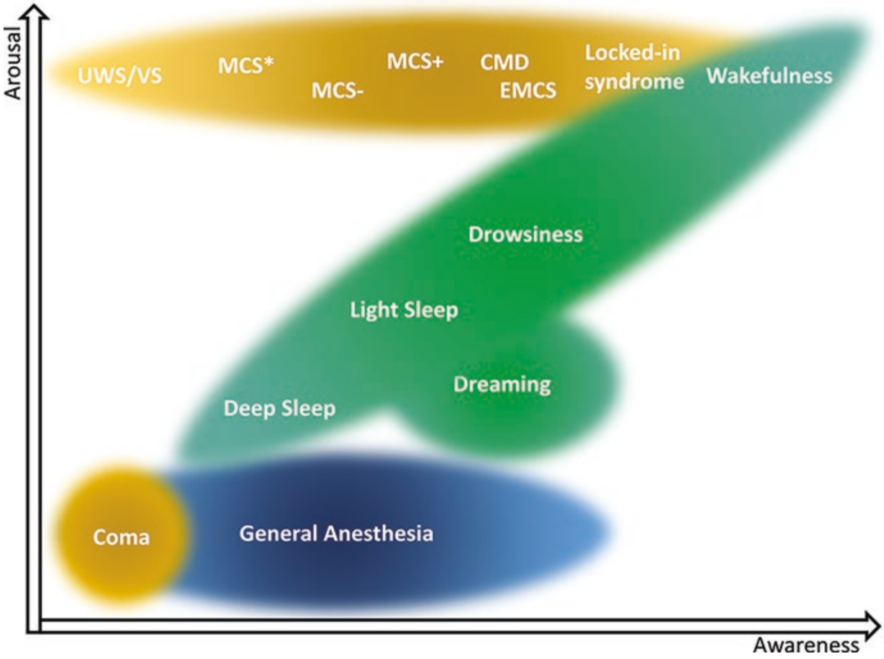

**Fig. 1.1** Level of arousal and awareness across physiological, pharmacological, and pathological states of consciousness. In physiological states of consciousness (green), arousal and awareness typically co-vary, with levels of arousal and awareness decreasing from wakefulness, to drowsiness, to light and deep sleep. During dreaming, awareness increases while arousal remains low. In pharmacological states of consciousness (blue), under general anesthesia, low levels of arousal are accompanied by varying levels of awareness, with a presumably considerable proportion of subjects presenting no awareness whatsoever, and with others having dream-like experiences or even awareness of the environment. In pathological states of consciousness and associated syndromes (yellow), arousal and awareness vary widely. Arousal and awareness are absent in patients in coma; after coma, patients regain arousal and may (or may not) regain awareness, from UWS/VS (no awareness) to MCS (fluctuating but reproducible signs of awareness, like, e.g., visual pursuit in MCS- or language-related behaviors such as command following in MCS+) to EMCS (recovery of awareness and communication). Note that while patients might appear as behaviorally unresponsive (i.e., behaviorally presenting as UWS/VS), neurophysiological testing might suggest partially to fully preserved covert awareness, as in the case of MCS*, CMD, or locked-in syndrome. Abbreviations: *CMD* cognitive motor dissociation, *EMCS* emerging from minimally conscious state, *MCS* minimally conscious state, *UWS/VS* unresponsive wakefulness syndrome/vegetative state

## Neurophysiological Techniques Used in the Study of the NCC

Neurophysiological techniques typically used to measure brain activity in the study of the NCC include positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and electroencephalography (EEG).

PET is a molecular imaging technique that allows for measurement of different biochemical processes of interest, with high biological specificity and good spatial resolution, in both cortical and subcortical structures. PET is most commonly used in combination with the fluoro-deoxy-glucose (FDG) tracer, to measure glucose metabolism. Glucose metabolism is the main substrate for energy in neurons and astrocytes and is directly linked to excitatory glutamatergic neurotransmission. Both absolute changes in brain global glucose consumption and relative changes in local glucose consumption can be assessed. Typically, relative decreases in local glucose metabolism, called hypometabolism, are investigated in the study of NCC.

fMRI is a functional imaging technique that allows for measurement of blood oxygenation, as indexed by the blood oxygen-level dependent (BOLD) signal, with good spatial and temporal resolution, in both cortical and subcortical structures. BOLD signal is indirectly coupled to neural activity via the hemodynamic response function. Co-fluctuations of BOLD signal across time are deemed as a proxy for synchronized neural activity, also known as “functional connectivity”. A way of describing the functional connectivity of brain regions is their organization in “brain networks”. Brain networks include, for example, the default mode and the executive control networks, which are of particular relevance in the study of NCC.

EEG is an electrophysiological technique that allows for measurement of voltage fluctuations via electrodes placed on the scalp, with extremely good temporal resolution. The typical parallel organization of cortical pyramidal neurons allows the summation of their postsynaptic potentials to reach fluctuations measurable through the scalp. As such, the number of synchronized neurons determines the energy of the measurable voltage on the scalp, while the rhythm of their synchronized firing determines its frequency. Classically, this can be analyzed on the scalp level as a power-spectral density, a curve that shows the energy across different frequency bands, typically delta (1–4 Hz), theta (4-8 Hz), alpha (8–12 Hz), beta (12–30 Hz), and gamma (>30 Hz). EEG has also been used for estimation of functional connectivity, either at electrode level or at the cortical level, using source reconstruction methods that allow for estimation of where the electrical signal in the brain originated. Finally, EEG has been used to investigate the complexity of activity in the brain. One example of this is the Perturbational Complexity Index (PCI), which is a quantification of the complexity of the brain response to transcranial magnetic stimulation (TMS).

## Physiological States of Consciousness: NCC in Sleep

Sleep is the most natural fluctuation in consciousness. It is widely preserved across the animal kingdom, and while its putatively essential function remains unknown [7], it has been associated with, for instance, plasticity and memory consolidation [8] or synaptic homeostasis [9]. Behaviorally, sleep manifests as periods of quiescence and reduced responses to the environment, which are coupled to profound changes in the state of the brain. As such, sleep is seen as a different state of consciousness compared to wakefulness [10]. The gold standard of tracking the neurophysiology of sleep is through polysomnography, which includes an EEG and other physiological signals such as heart beat, respiration, and muscle tension [11]. During a sleep cycle, the brain goes through several stages at approximately 90 min per cycle [12]. The cycle starts with a transition from wakefulness to non-rapid eye movement (NREM) stage 1, marked by a significant slowing of the EEG with the disappearance of alpha (8–12 Hz) oscillations, and is deemed light sleep in terms of consciousness [11]. Sleep, and thus potentially unconsciousness, is deepened in NREM2, which is characterized by further EEG slowing and the appearance of sleep spindles, a waxing and waning waveform of 12–16 Hz, and K-complexes, large amplitude waves of a short negative and longer positive deflection. The deepest stage of sleep is NREM3 where the EEG is dominated by large-amplitude slow oscillation (<4 Hz) and is usually associated with reduced glucose metabolism compared to wakefulness. REM sleep usually occurs at the end of the 90-minute cycle and exhibits wake-like desynchronized EEG in the theta frequency range (4–8 Hz), rapid eye movements and increased metabolic activity in some parts of the brain [13].Vivid dreaming has traditionally thought to occur predominantly during this-stage. However there is now extensive evidence that dreaming also occurs during NREM sleep; dreaming is in fact reported in upto 70% of awakenings from this stage [14]. The complexity of the response of the brain to TMS stimulation during deep sleep (i.e., NREM3) is reduced compared to wakefulness, while the response during REM sleep is more similar (but not identical) to wakefulness [15]. These differences are likely the result of altered, effective long-range connectivity. The activity and connectivity in the default mode network also reduces along the NREM sleep cycle [16].

The neural correlates of consciousness have typically been assessed in sleep studies by contrasting the states of wakefulness and NREM sleep. Studies using this approach have highlighted the importance of the activity of the thalamocortical loop, which interacts with the ascending reticular activating system (ARAS), located in the brainstem [10, 17]. Yet, this contrast travels along both the awareness and arousal dimensions of consciousness, making it hard to distinguish the proper NCC from the background conditions of consciousness, like potentially the ARAS, that might facilitate cortical excitability to support awareness, but not directly contribute to it. At the forefront of solving this issue (cf. a recent review on theories of consciousness [18]), is the serial awakening paradigm. This paradigm assumes that arousal varies minimally across sleep states, in contrast to the presence of a conscious experience. Both during NREM and REM sleep, presence of conscious experiences can be investigated after awakening the subject to provide a retrospective report [19]. Contrasting instances of reported awareness and reported absence of awareness, in both REM and NREM sleep, allows for the distillation of the NCC that are specifically related to awareness, independent of arousal. According to the results by Siclari and colleagues, these NCC are located in temporo-occipital-parietal cortical regions, including the precuneus and posterior cingulate cortices. Of note, while these within-state paradigms in sleep show great promise, their implementation can be far from trivial [20].

As will become clear in this chapter, DoC patients also represent an interesting avenue for the research into the NCC. Theoretically, sleep studies to assess the NCC can be performed in this population as long as an independent marker of sleep is provided, e.g., by assuming that eye opening/closure in DoC patients is related to the sleep/wake cycle or by using actigraphy as an objective proxy [21]. The neurophysiology of sleep in DoC can, however, be markedly different from neurologically intact subjects, with periods of eye closure not associated with any EEG marker of sleep, or on the contrary markers of sleep intruding into periods of eye opening [22]. In general, the hallmarks of sleep are found less often in states with lower consciousness [23]. These results raise challenging questions on the nature of sleep in this population, and on how sleep might interact with the DoC itself, a question that becomes particularly relevant when using this patient population to search for the NCC.

Studying NCC through sleep has many advantages, including its widespread availability and lack of side effects, and the variate spectrum of arousal and awareness levels it explores (Fig. 1.1). Still, there are also certain pitfalls to be considered. For instance, methodological challenges in the search for NCC based on sleep do exist, in the first place in the definition of sleep stages. As an example, NREM3 sleep is defined by sleep-scoring rules based on an arbitrary amplitude threshold. Whether such a threshold is reached depends, however, on the number of pyramidal neurons available, where a minimum number of neurons is necessary for their summed activity to actually be able to cross said threshold. In case of brain damage, as in DoC populations, the number of pyramidal neurons available might be too limited, so that NREM3 sleep might not be detected, even if present. These kinds of considerations are also in place for "within-state" investigations, where the state, for instance NREM2, is imposed based on well-researched but semi-arbitrary, subjective visual scoring rules. Finding differences within these states is useful for NCC research, but also questions the meaning of the boundaries based on which the original state was defined in the first place. Yet, this is also the way forward, where better definition of the NCC can aid in defining states of sleep, and determining their presence in health and disease.

## Pharmacological States of Consciousness: NCC in Anesthesia

The practice of administering drugs to induce a state of general anesthesia in order to perform surgery dates back 177 years [24]. This practice revolutionized surgery and constitutes one of the cornerstones of modern medicine. Depending on the specific requirements of the surgery, general anesthesia may include varying degrees of (reversible) analgesia, amnesia, paralysis, and unconsciousness. These behavioral states are reached and exited gradually, in a process that can be divided into three main phases, each corresponding to different depths of anesthesia and distinguished by specific physiological and behavioral signs: induction, maintenance, and emergence [25]. The phase of induction covers the transition from wakefulness to the sedated state: patients are behaviorally unresponsive but usually easily arousable, with eyes closed and in spontaneous ventilation [25, 26]. As the induction phase progresses and the depth of anesthesia increases, the patient's heart rate starts to rise and episodes of respiratory depression become more frequent, making breathing support devices necessary [25, 26]. Cessation of eye movements, progressive paralysis, and respiratory depression characterize the maintenance phase, also known as surgical anesthesia, as in this period surgical operations may be performed. Return of spontaneous respiration signals the beginning of emergence from anesthesia. Heart rate and blood pressure begin to return to pre-anesthetic levels, and behavioral responsiveness is gradually recovered [25, 26]. The duration of each of these phases is highly variable and depends on a combination of factors such as the anesthetic agents used and their dosage, the type of surgical operation, and the patient's characteristics [25].

General anesthesia is induced and maintained via a primary sedative-hypnotic agent (general anesthetic) in combination with auxiliary agents such as sedatives, analgesics, and neuromuscular blocking drugs [26]. Intravenous general anesthetics (e.g., propofol, ketamine, dexmedetomidine) are typically used for general anesthesia induction and inhalational anesthetics (e.g., volatile liquids such as desflurane, isoflurane, and sevoflurane) for general anesthesia maintenance [26]. To induce anesthesia, anesthetic agents are thought to promote neural inhibition and/or reduce neural excitation by interacting with ion channels located in cortical regions, the brainstem, and thalamic nuclei [24]. Some common mechanisms of action include potentiation of γ-aminobutyric acid type A ($\text{GABA}_\text{A}$) receptors in combination with inhibition of glutamate receptors such as α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) or *N*-methyl-D-aspartat (NMDA). As each anesthetic has a distinct pharmacodynamic profile, which changes considerably depending on the dosage, the effects of anesthetics on the brain vary considerably. However, some neural mechanisms seem to be shared by several anesthetic agents, including an increase in EEG slow/delta and alpha oscillations (cf. [25, 27]); a decrease in fMRI/EEG functional and effective connectivity between frontal and parietal regions (cf. [25, 27]) and an overall decrease in complexity of cortical dynamics [28]; a fragmentation of hippocampal network dynamics (measured via extracellular recordings) [29]; a progressive isolation of primary sensory regions from higher-order ones, as seen using fMRI functional connectivity, and a generalized change in the topological properties of brain networks, e.g., from lower to higher modularity (i.e., estimated decomposition of networks into modules) [30].

A substantial proportion of existing anesthesia studies have investigated the NCC by contrasting general anesthesia with wakefulness. Yet, this comparison is inherently confounded by the diversity of these two conditions, which are physiologically different, e.g., in terms of arousal (similar to the case of sleep; see above). As for sleep, it is possible to account for these confounders by using no-task, within-state paradigms. Instead of regarding the anesthetic state as a “homogeneous” state of unconsciousness, these paradigms take into account that consciousness (spontaneously) fluctuates during general anesthesia. Indeed, while anesthetized participants might be thought of as unconscious based on lack of behavioral responsiveness or post-anesthesia explicit recall of (intraoperative) experiences, it has now been widely shown that unresponsiveness or lack of explicit recall does not necessarily imply unconsciousness [31, 32]. Studies using the isolated forearm technique (IFT), which, by preventing muscle relaxants from acting on one of the forearms, assesses responsiveness during general anesthesia in real time, revealed that up to 34.8% of anesthetized patients were conscious of their surroundings (i.e., “environmentally” connected conscious) (cf. [31]). In these studies, most of the IFT respondents could not remember the intraoperative (conscious) event after emergence from general anesthesia, consistently demonstrating that intraoperative connected consciousness is not necessarily tied to explicit recall. Additional studies have also estimated that intraoperative dreaming (i.e., disconnected consciousness) occurs in 22–58.6% [33] of patients during general anesthesia. These studies evidenced the necessity to decompose (conscious-related) anesthetic effects into several components: consciousness (i.e., subjective experience, like dreaming), (dis)connectedness (i.e., (un) consciousness of the environment), and responsiveness (i.e., spontaneous and/or goal-directed behavior). The NCC identified from previous general anesthesia studies, which regarded anesthesia as a continuous state of unconsciousness, could therefore reflect (dis)connected consciousness, unconsciousness, neither of them, or both.

As in the case of sleep, a promising approach to distinguish between these different components is the use of serial awakening paradigms to collect retrospective reports: with this approach, (unresponsive) anesthetized participants are awakened and questioned about the experience they were having immediately prior to awakening. As subjects are questioned multiple times *during* anesthesia, the lack of explicit recall is minimized. By separating conscious and unconscious states on the basis of the collected reports (and not (un)responsiveness), NCC during anesthesia can be investigated within-state. A growing number of studies are beginning to implement such paradigms. For example, a recent EEG study [34] in healthy participants sedated with dexmedetomidine or propofol differentiated episodes of connected consciousness, disconnected consciousness, and unconsciousness that occurred during the period of unresponsive sedation. The contrast between (disconnected) consciousness and unconsciousness revealed a reduction in beta/delta ratio in anterior and posterior cingulate regions of the default mode network, as one of the main markers of unconsciousness, highlighting the importance of these areas for conscious experience.

In conclusion, anesthesia is a fundamental component of modern medicine, whose pharmacokinetics and pharmacodynamics have been extensively studied. As it causes spontaneous fluctuations in consciousness, it makes an excellent candidate for the study of NCC with no-task, within-state paradigms. However, to avoid conflating conscious and unconscious states, attention must be paid to how consciousness is assessed. Recent studies have successfully adopted innovative methods to overcome previous limitations and hold the potential to contribute to the search for the "real" NCC, separating NCC from its consequences and background conditions.

## Pathological States of Consciousness: NCC in Disorders of Consciousness

DoC include several conditions with varying degrees of arousal and absent or limited awareness. *Coma* is a temporary state characterized by absence of arousal and awareness, and characterized behaviorally by absence of eye-opening (both spontaneous and following stimulation). Coma persists for more than 1 h and typically not more than 1 month. A patient exits coma when eye opening is regained, progressing to either *unresponsive wakefulness syndrome/vegetative state (UWS/VS),* characterized by reflexive motor behavior but lack of purposeful motor behavior or cognitive functions, or to *minimally conscious state (MCS)*, characterized by non-reflexive and purposeful behavior. When behavioral signs point to a recovery of perceptual awareness, the patient is diagnosed as MCS−, while if behavioral signs point to a recovery of language comprehension, the patient is diagnosed as MCS+. If the patient improves further and regains functional communication or functional use of objects, (s)he is diagnosed as *Emerging from the MCS (EMCS), which* is not considered as part of the spectrum of DoC. A patient in EMCS is deemed fully conscious, while, however, retaining varying degrees of motor and cognitive disability.

Several studies have investigated brain activity alterations in DoC. PET studies have shown that brain glucose metabolism, globally, is extremely diminished in DoC patients, with stronger metabolic decreases in patients with more severe consciousness impairment [35]. Some specific regions were found to be most consistently hypometabolic, including the precuneus, cingulate, and angular gyri (forming the internal awareness or default mode network) and lateral fronto-parietal areas (forming the external awareness or executive control network) [36, 37] (Fig. 1.2). fMRI studies in DoC patients have shown extensive functional connectivity alterations within regions of the internal awareness/default mode network [38], as well as in the external awareness/executive control network and sensory networks [39], and across networks [40]. EEG studies in DoC patients have instead shown increased slow EEG oscillations, with increased delta power [41] and decreased alpha power [42], which might indicate increased local processing and decreased cortico-thalamic integration [43]. Studies using EEG combined with TMS to quantify complexity of brain activity given a standardized perturbation in brain activity, as induced by TMS, have shown that brain complexity is systematically decreased in DoC, the degree of reduction in complexity mirroring the level of consciousness of brain-injured patients [28].

As in the case of sleep or anesthesia, the study of NCC based on DoC typically relies on a contrastive approach, where patients in a state of unconsciousness are compared to subjects that are conscious or have regained consciousness. The advantage of studying NCC based on disorders of consciousness is that (with the exception of coma) it allows for the study of states in which arousal and awareness are dissociated, making it possible to distinguish between neural activity related to arousal and neural activity directly related to awareness [6]. Studies investigating NCC in DoC have typically compared, cross-sectionally, patients with different levels of consciousness impairment either against neurologically intact volunteers or among each other. The latter approach, comparing in particular UWS/VS vs. MCS patients, is deemed particularly promising, as it allows for the isolation of consciousness-related differences in brain activity, while minimizing spurious differences due to other consciousness-unrelated brain damage [5]. A cross-sectional, multimodal PET-MRI study by Di Perri et al. [38] in UWS/VS, MCS, EMCS, and healthy volunteers has shown consciousness-level-dependent increases in functional connectivity of the default mode network and in brain metabolism of fronto-parietal regions [38] (Fig. 1.2). Some longitudinal studies also exist, where brain activity is contrasted across different time points, within the same patients, as they evolve along different states of consciousness. One recent longitudinal study in UWS/VS and MCS patients has shown that improvement in the level of consciousness was associated with reductions in theta power and increase in functional connectivity in the alpha band [44], possibly indicating progressive recovery of thalamo-cortical integration.

An important caveat of studying NCC based on DoC is that DoC patients are, obviously, unable to provide a report concerning their state of consciousness. The state of consciousness of a DoC patient is therefore inferred indirectly, typically based on behavioral cues expressed by the patient. Such inference relies on the assumption that the behavioral response produced by a patient is representative of the patient's actual state of consciousness, and that the former is not limited by whatever sensorial, cognitive, or motor deficit a patient with extensive brain damage might present [45]. Still, it is now well known that a certain dissociation between behavioral responsiveness and state of consciousness exists, and that *covert* consciousness in apparently unresponsive patients is possible. This case is well exemplified by *locked-in syndrome (LIS)* patients, who have intact consciousness despite being partially or totally behaviorally unresponsive, and by *cognitive motor dissociation (CMD)* [46] and *minimally conscious state* (MCS*)* [47, 48], where covert conscious behaviors like covert command following or cerebral function possibly indicative of consciousness, respectively, are present in otherwise unresponsive patients. To overcome such limitations, some recent studies have adopted a different approach, trying to bypass the limitations of a definition of consciousness based on

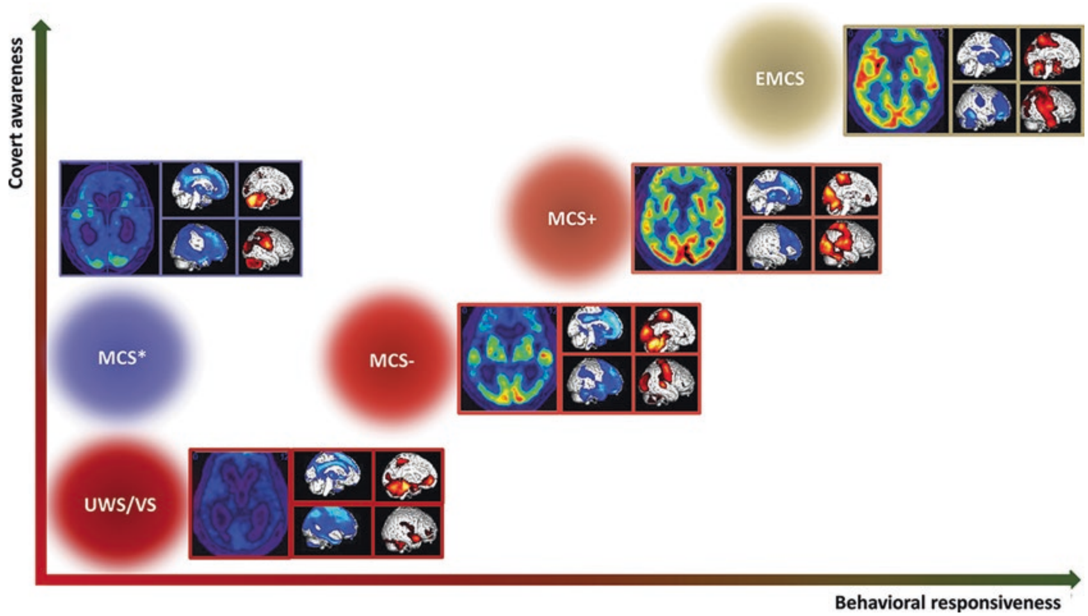

**Fig. 1.2** Alterations of brain glucose metabolism in severely brain damaged patients after coma. The figure shows alterations of brain glucose metabolism in severely brain damaged patients with prolonged UWS/VS, MCS*, MCS−, MCS+, and EMCS. Alterations in brain glucose metabolism are observed both at global and local level. A generalized, global decrease in brain glucose consumption, of around 40–70% compared to healthy awake volunteers, is typically present (axial brain renders, left section of each panel). The most severe decreases in brain glucose metabolism occur in medial and lateral fronto-parietal regions and in the thalamus and the caudate nucleus (statistical maps on 3D brain renders, right section of each panel, blue). Presence of regions with relatively preserved glucose metabolism is possible, with some topographical variability across patients (statistical maps on 3D brain renders, right section of each panel, red). While alterations in brain glucose metabolism tend to mirror the degree of behavioral responsiveness of the patient, a proportion of behaviorally unresponsive patients show milder alterations in glucose metabolism than expected in a behaviorally unresponsive patient. Based on this PET evidence, these patients (MCS*) are suspected to have some degree of covert awareness. Abbreviations: *EMCS* emerging from minimally conscious state, *MCS* minimally conscious state, *UWS/VS* unresponsive wakefulness syndrome/vegetative state

behavioral responsiveness, by using previously tested neuroimaging and neurophysiological markers for consciousness, as indicators of the conscious state of DoC patients. A previous study [49] combining measures of perturbational complexity and brain metabolism in UWS/VS patients revealed preserved metabolic rates and high complexity levels in almost half of the unresponsive patients. A more recent study [48] has likewise shown that almost two thirds of patients behaviorally diagnosed as fully unconscious at the bedside (i.e., UWS/VS) demonstrate residual brain metabolism in areas of the internal or external awareness networks [48]. The authors suggest that these findings might point to the presence of internal or external awareness in these patients, who, accordingly, have a higher likelihood of regaining consciousness at follow-up [48]. While these studies have clear clinical implications, a theoretical framework for how to leverage these findings to advance the understanding of the NCC is still lacking.

## Conclusions

In recent decades, advances in neuroimaging and neurophysiology have allowed us to measure brain activity across different states of consciousness, letting us obtain unprecedented insights into the neural mechanisms underlying sleep, anesthesia, and disorders of consciousness. As the research in the field progresses, the design of study protocols to investigate NCC is becoming more refined. In the field of sleep and anesthesia, studies using coarser between-state contrastive approaches are progressively being replaced with studies relying on more precise within-state paradigms. In the field of DoC, the degree of detail in describing consciousness states is advancing, with the clinical categories of coma and UWS/VS, that just 20 years ago covered the full taxonomy of DoC [6], being now accompanied by entities such as MCS−, MCS+, MCS*, and CMD, that better capture the variability of the states of consciousness within the DoC spectrum.

Still, the identification of neural mechanisms underlying consciousness remains challenging in DoC, as our current measurement of (presence or absence of) consciousness heavily relies on subjective reports and behavioral responsiveness, both of which can be impaired in DoC (due to lack of arousal or presence of cognitive, sensory, or motor deficits). Progresses in this direction might come from the use of independent and objective measures of consciousness in DoC, for example using markers of neural activity that are tested and validated based on comparisons across different (physiological, pharmacological, and pathological) states of consciousness (see, e.g., [28]). Indeed, integration and cross-validation of findings across sleep, anesthesia, and DoC will likely be key to advance further in the identification of the neural mechanisms of consciousness [50]. Encouragingly, and as highlighted in the current chapter, some findings do seem to converge across different states of consciousness, with studies in DoC, sleep, and anesthesia reporting changes in brain activity of the default mode network (at least, in its posterior regions) as well as global changes in brain complexity, in association with states of (un) consciousness.

As the research in the field of NCC continues, progress is also being made from a theoretical point of view, thanks to ongoing initiatives that are systematically and rigorously testing competing theories of consciousness (see [51]). Perfecting current theories of consciousness and producing a coherent theoretical framework for understanding consciousness will likely be a fundamental step to guide design of future study, development of new experimental paradigms, and interpretation of empirical findings [18]. Overall, the search for the NCC is far from over (see also "The Decades-long bet on consciousness ends," https://www.nature.com/articles/d41586-023-02120-8). Still, while the road to the identification of NCC is long, the path is becoming clearer.

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# Chapter 2
# Behavioral Assessment and Diagnosis of Disorders of Consciousness

**Caroline Schnakers and Katherine O'Brien**

**Abstract** Behavioral assessment remains the critical modality for the detection of signs of consciousness and, hence, for identifying states of altered consciousness after brain injury. However, because of the presence of confounding factors such as severe functional, motoric and cognitive impairment, accurate diagnosis is a challenging enterprise, leading to serious consequences for a patient's ongoing care. In this review, we will describe the behavioral characteristics of the different levels of consciousness in the recovery continuum. We will describe methods for behavioral assessment of consciousness at the bedside, and discuss the existing frameworks that help clinicians in formulating an accurate assessment.

## Introduction

Disorders of consciousness and severe brain injury have garnered a lot of attention in recent years. Due to progress in intensive care, more and more severely brain-injured patients survive their initial brain insult. Although they only account for a small percentage of all brain injuries, severe brain injuries come with a large cost (approximately US$4 billion per year in direct medical costs) due to their need for long-term care [1]. It is commonly believed that severe brain injuries result in poor

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C. Schnakers (✉)
Research Institute, Casa Colina Hospital and Centers for Healthcare,
Pomona, CA, USA
e-mail: cschnakers@casacolina.org

K. O'Brien
TIRR Memorial Hermann Hospital, Houston, TX, USA

Department of Physical Medicine and Rehabilitation, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, TX, USA

Department of Physical Medicine and Rehabilitation, Baylor College of Medicine, Houston, TX, USA
e-mail: katherine.obrien@memorialhermann.org

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outcomes, but recent research has shown this to be untrue. Around 65% of patients with severe brain injuries who cannot respond to commands at the time of discharge from inpatient rehabilitation can function independently (for mobility and self-care) after 10 years post injury [2, 3]. Many of these patients will progress through the spectrum of disorders of consciousness over time but only a small proportion make it to the appropriate setting for the subtle changes to be recognized. Some of these cases have received important coverage 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 was found to be emerged from a minimally conscious state 19 years (1984–2003) after a severe traumatic brain injury [4]. At the same time, prolonged hospitalization is expensive. Inevitably, questions regarding end-of-life decisions are brought up both acutely and in more chronically injured patients. The social, economic, and ethical consequences associated with disorders of consciousness are enormous. There are also vast differences in people's interpretations of meaningful recovery or quality of life based on the level of consciousness, making accuracy in diagnosing level of consciousness imperative.

In this context, to improve care for these patients and facilitate scientific research, the American Academy of Neurology (AAN) and the European Academy of Neurology (EAN) have published the first guidelines to help clinicians assess and care for patients with acute and prolonged (>28 days) disorders of consciousness (DoC) [5, 6]. Indeed, patients with DoC require specialized care and assessment. At least 3 of the 18 AAN recommendations address behavioral assessment of consciousness while all EAN recommendations address this topic. Accurate behavioral assessment requires expertise on behalf of the clinician as there is no true measure of consciousness but more an assessment of behavioral proxies. The clinician will be observing the patient's spontaneous behaviors and their reactions to stimuli occurring in their environment and deciphering the patient's level of consciousness. The clinician's mindset and biases can greatly impact the result of a behavioral assessment. It also depends on the physical (neuromuscular) and mental capacities (particularly, the arousal 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%) [7, 8]. The accuracy of the assessment is, however, crucial clinically, psychologically, legally, and ethically. It influences the way the patient's care will be oriented. Developing and administering valid and sensitive behavioral scales to detect the presence of signs of consciousness, even subtle, therefore represents a significant 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. 2.1 and Table 2.1). This state usually results either from a lesion limited to the brainstem (involving the reticular activating system) or from global brain dysfunction (most often caused by bihemispheric, 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 confusion, or delirium. Prolonged coma is rare as this condition typically resolves within 2–4 weeks, most often evolving into vegetative state or minimally conscious state [10]. It is worth noting that being in a coma is different from being brain dead. The term brain death requires a bedside demonstration of irreversible cessation of all functions of the brain, including brainstem functions, for

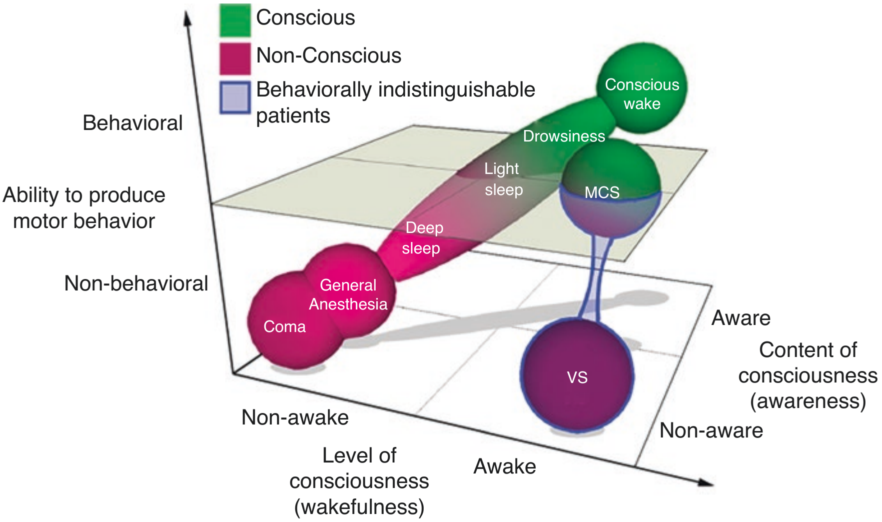

**Fig. 2.1** The conundrum of consciousness. Disorders of consciousness are defined by two main components: the level of consciousness and the content of consciousness. This figure illustrates where different states (i.e., coma, vegetative state—VS, minimally conscious state—MCS but also states related to sleep and anesthesia) are placed on both continuums. It also represents where patients with covert cognition would be placed. (Reprinted from [69] with permission from Annual Reviews, Inc.)

**Table 2.1** Comparison of the behavioral features of coma, VS, MCS−, MCS+, emergence from MCS (EMCS) and covert awareness (CA)

| | Coma | VS | MCS− | MCS+ | EMCS | CA |
|---|---|---|---|---|---|---|
| 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 | Startle |
| Affective response | None | Random | Contingent | Contingent | Contingent | Random |
| Response to command | None | None | None | Reproducible | Consistent/reproducible | Consistent/reproducible (as detected by neuroimaging or electrophysiology) |
| Verbalization | None | None | Random vocalization/none | Intelligible words | Intelligible words | None |
| Communication | None | None | Unreliable | Unreliable | Reliable | Unreliable/reliable as detected by neuroimaging or electrophysiology) |