Severe Brain Damage: Coma and Related Disorders of Consciousness

132

Olivia Gosseries and Steven Laureys

Contents

Abstract

Progress in intensive care efforts has increased the number of patients who survive severe acute brain damage. Although the majority of these patients recover from coma within the first days after the insult, some permanently lose all brain function (i.e., brain death), while others evolve to an unresponsive wakefulness syndrome or a minimally conscious state. A nosological classification now clearly defines these different altered states of consciousness and their diagnostic clinical signs. The behavioral evaluation is the primary way to assess patients' level of consciousness, even though sensorimotor impairments, aphasia, or fluctuations of vigilance levels can conceal the presence of

O. Gosseries (✉) · S. Laureys
Coma Science Group, GIGA Consciousness & Centre du Cerveau, University Hospital and University of Liège, Liège, Belgium
e-mail: ogosseries@uliege.be; steven.laureys@uliege.be

D. W. Pfaff et al. (eds.), *Neuroscience in the 21st Century*,
https://doi.org/10.1007/978-3-030-88832-9_95

consciousness. Functional neuroimaging and electrophysiology studies are changing our understanding of patients with coma and related states and more generally on the neural correlates of consciousness. These new tools are used to complement the clinical diagnosis and help assess patients more accurately. Some severely brain-damaged patients may thus show residual cortical processing in the absence of any behavioral signs of consciousness. Treatments are still scarce, but recent avenues include pharmacological interventions and noninvasive brain stimulation techniques. Ethical issues, end-of-life decision, pain, and quality of life are also some of the challenges clinicians face when working with this fragile population.

Keywords

Coma · Brain injury · Brain death · Near-death experiences · Vegetative state · Minimally conscious state · Locked-in syndrome · Consciousness · Unresponsive wakefulness syndrome · Awareness · Arousal · Responsiveness

Brief History

Progress in intensive care efforts has increased the number of patients who survive severe acute brain damage. Although the majority of these patients recover from coma within the first days after the insult, some permanently lose all brain function (i.e., brain death), while others evolve to a state of "vegetative" unresponsive wakefulness. Those who recover typically progress through different stages before fully or partially recovering consciousness. When "vegetative"/unresponsive patients show minimal signs of consciousness but are unable to reliably communicate, the term "minimally conscious state" (MCS) is used. A subcategorization of MCS was proposed based on the presence or absence of residual language processing: MCS+ when patients present command-following, intelligible verbalization and/or intentional communication, and MCS- when patients show non-related language responses, such as visual pursuit, automatic motor responses, and localization of noxious stimuli. Functional neuroimaging and electrophysiology studies are changing our understanding of patients with coma and related states. Some severely brain-damaged patients may show residual cortical processing in the absence of behavioral signs of consciousness. These patients who show nonmotor-dependent evidence of consciousness or communication, only assessable via paraclinical testing (e.g., functional magnetic resonance imaging (MRI) or evoked potentials), are considered to be in a non-behavioral MCS (MCS*), also referred to as "cognitive-motor dissociation" (CMD), "functional locked-in syndrome," or "cover consciousness" (there is no consensus yet on how to call this category of patients). An improved assessment of brain function in coma and related states is not only changing nosology (Fig. 1) but also offers a better-documented diagnosis and prognosis and helps to further identify the neural correlates of human consciousness.

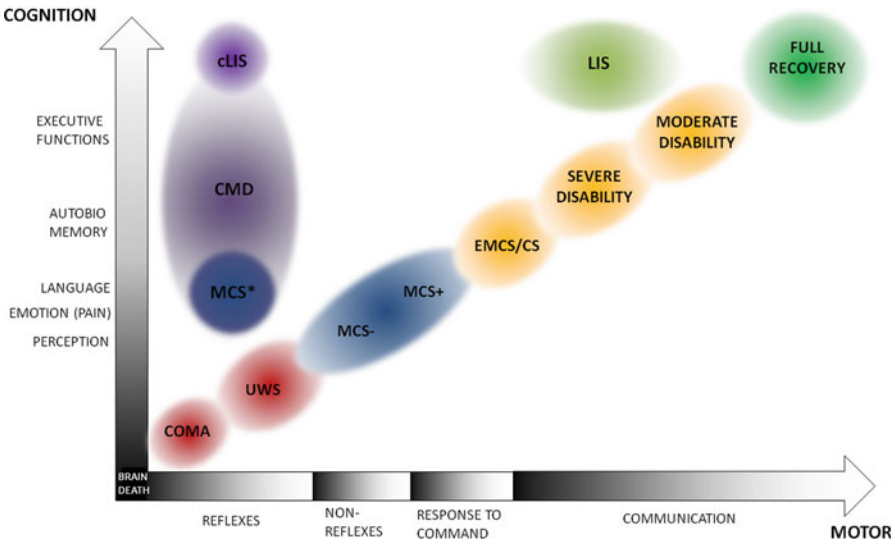

Fig. 1 Proposed nosology of the diagnostic entities than can be encountered following a severe brain injury, based on motor and cognitive functions. Red circles represent patients who are unconscious (coma and unresponsive wakefulness syndrome (UWS)), blue circles patients in a minimally conscious state (MCS), and yellow circles patients who can communicate (emergence from the MCS (EMCS); CS, conscious state). Dark green circle illustrates full recovery and light green circle the locked-in syndrome (LIS). Dark purple represents cognitive-motor dissociation and dark blue circle the minimally conscious state*. Light purple circle illustrates the rare case of complete locked-in syndrome (cLIS, diagnosed via neuroimaging examinations). The black-to-white gradient represents the evolution from absence (black) to the recovery of a behavior (white). (Taken from Thibaut et al., Lancet Neurology, 2019)

Measuring Consciousness

There is at present no satisfactory, universally accepted definition of consciousness. For the purposes of clinical neurosciences, consciousness consists of two basis components: *wakefulness* (i.e., arousal or vigilance) and *awareness* (i.e., content of consciousness). Awareness in turn can be divided into *external* awareness (i.e., sensory or perceptual awareness of the environment) and *internal* awareness (i.e., stimulus-independent thoughts, mental imagery, inner speech, daydreaming, or mind wandering). Figure 2 shows that in normal physiological states, level of arousal and awareness (environmental and self) are usually positively correlated. You need to be awake in order to be aware (rapid eye movement or REM sleep and lucid dreaming being notorious exceptions). Patients in pathological or pharmacological coma (i.e., general anesthesia) are unconscious because they cannot be awakened. The unresponsive wakefulness syndrome is a dissociated state of consciousness (i.e., patients being seemingly awake but lacking any behavioral evidence of non-reflex behavior or command-following). Other examples of dissociation

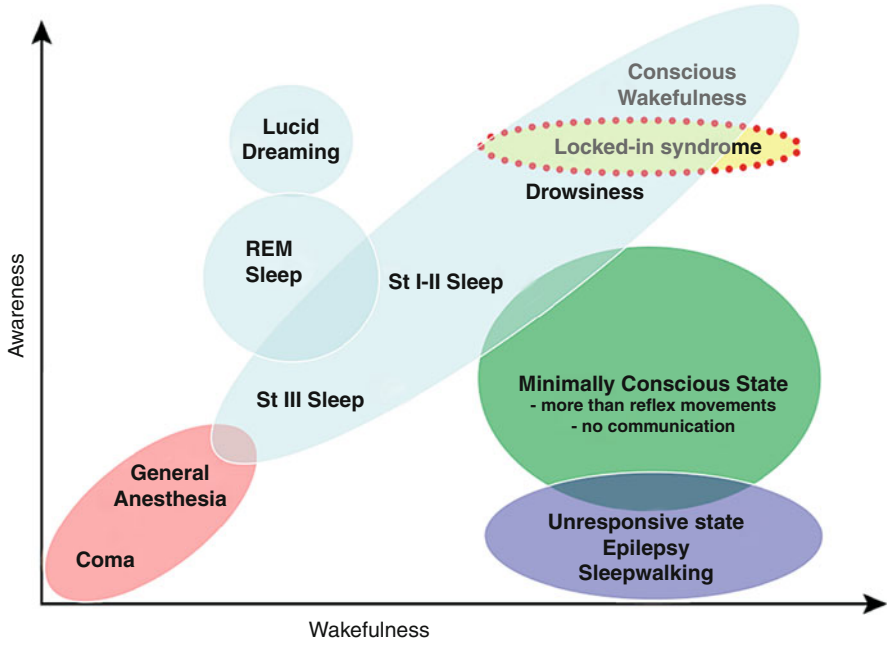

Fig. 2 Wakefulness or arousal usually positively correlates with awareness as illustrated in the case of normal physiological modifications of consciousness during sleep (with the exception of the oneiric activity during REM sleep). Patients in pathological or pharmacological coma (i.e., general anesthesia) are considered unconscious because they cannot be awakened. The unresponsive wakefulness syndrome illustrates the dissociation between wakefulness and awareness. In the locked-in syndrome, patients are unable to move and express their awareness except via eye-coded communication

between the presence of reflex movements in the absence of command-following can be encountered in sleepwalking and in some form of epilepsy (absence and complex partial seizures). Recently, the concept of "responsiveness" has emerged as a new component to take into account in consciousness research. Responsiveness corresponds to behavioral interactions with the environment (excluding reflex behavior) and thus is what is observed when assessing patients with severe brain injury. However, responsiveness does not always equate awareness, as, for example, demonstrated with patients in complete locked-in syndrome who are unable to move and yet are fully conscious.

Bedside evaluation of residual brain function in severely brain-damaged patients is difficult because motor responses may be very limited or inconsistent. In addition, consciousness is not an all-or-none phenomenon, and its clinical assessment relies on inferences made from observed responses to external stimuli at the time of the examination and thus their behavioral responsiveness. How do we quantify consciousness at the bedside? Clinically, arousal will simply be assessed by examining the presence of spontaneous or stimulus induced eye-opening and the presence of

reproducible command-following will be taken as proof of (external) awareness. Additionally, the presence of spontaneous or induced non-reflex behaviors, such as visual pursuit or localization to noxious stimulations, will be considered as evidence of (minimal) consciousness. The bedside examination of consciousness in severe brain-damaged patients often is very challenging because observed movements may be very small, inconsistent, and easily exhausted, potentially leading to diagnostic errors. Repeating behavioral evaluations is therefore highly recommended to reduce this risk of misdiagnosis.

The "Glasgow Coma Scale" is the most widely used standardized bedside tool to quantify wakefulness and awareness in coma. It was devised as a formal scheme to overcome the ambiguities that arose when information about comatose patients was presented and groups of patients compared. The scale has three components: eye, verbal, and motor response to external stimuli. The best or highest responses are recorded. The presence of spontaneous eye-opening indicates that the arousal mechanisms of the brainstem are active. The presence of verbal responses indicates the restoration of a high degree of interaction with the environment (i.e., awareness). The motor response first assesses whether the patient obeys to simple commands, given in verbal, gestural, or written form. If there is no response, a painful stimulus is applied. Stereotyped flexion responses are the most common of the motor reactions observed in patients with severe brain injuries; they are also the most enduring. Extensor posturing is more easily distinguished and is usually associated with adduction, internal rotation of the shoulder, and pronation of the forearm. The term "decerebrate" and "decorticate" rigidity should be avoided because it implies a specific physioanatomical correlation, known to be not necessarily correct. It is tempting to sum the three components of the Glasgow Coma Scale into a total score, ranging from 3 to 15. However, given the increased use of intubation, ventilation, and sedation of patients with impaired consciousness before arrival at hospital, patients might wrongly being scored as GCS 3/15 rather than being more appropriately reported as impossible to assess or score. One of the most frequently expressed reservations regarding the scale has been its failure to incorporate brainstem reflexes. Many coma scales that include brainstem indicators have been proposed (e.g., the Glasgow Liège Scale and the Full Outline of Unresponsiveness), but none are as extensively used as the Glasgow Coma Scale. Another drawback of the GCS is its lack of assessment of signs of consciousness. For instance, visual pursuit is not assessed, but it is one of the first conscious behaviors to recover after coma. Visual pursuit is however assessed with the Full Outline of Unresponsiveness.

After the acute setting, when patients have emerged from their coma and the difference needs to be made between unresponsive or minimally conscious patients, Glasgow Coma Scale assessment should be replaced by other scales. For chronic disorders of consciousness, the most validated scale is the Coma Recovery Scale-Revised (CRS-R). This scale assesses auditory, visual, verbal, and motor functions as well as communication and arousal level (the total score ranges between 0 and 23). It has shown superior performance in detecting minimal signs of consciousness after the period of coma as compared to other scales or unstructured assessment. Several studies showed that the clinical consensus diagnosis could be

incorrect in up to 40% of patients considered to be "vegetative" if not assessed with the CRS-R. As we will see, locked-in syndrome patients may also be mistakenly considered unconscious. The problem of assessing consciousness in severe brain damage may be further complicated when patients have underlying deficits in the domain of verbal or nonverbal communication functions, such as aphasia, agnosia, or apraxia.

Recently, a new scale was developed, the Simplified Evaluation of CONsciousness Disorders (SECONDs), which can be used both in acute and chronic settings (Fig. 3). The SECONDSs allows any clinicians to diagnose patients with disorders of consciousness in a short time and without extensive training. In addition to arousal, this scale assesses the most frequently observed signs of consciousness among patients recovering from coma: command-following, visual pursuit, visual fixation, pain localization, oriented behaviors, as well as communication. This tool is 2.5 times faster than the CRS-R (7 versus 17 min). Overall, the SECONDs appears to be a more convenient tool to assess the level of consciousness in patients, which can be easily implemented in clinical and research settings to significantly decrease misdiagnosis and optimize treatment decisions.

Coma

Coma is characterized by the absence of arousal and awareness. It is a state of unarousable unresponsiveness in which the patient lies with the eyes closed and shows no signs of awareness. The patient lacks the spontaneous periods of wakefulness and eye-opening induced by stimulation that can be observed in the unresponsive wakefulness syndrome. The most frequent causes of coma are traumatic or ischemic brain damage. It can result from diffuse bihemispheric cortical (e.g., after cardiac arrest) or white matter damage secondary to diffuse neuronal or axonal injury (e.g., after deceleration traffic accidents) or from focal but extensive brainstem lesions (e.g., after stroke or hemorrhage). To be clearly distinguished from syncope, concussion, or other states of transient unconsciousness, coma must persist for at least 1 h.

In general, comatose patients who survive begin to awaken and recover gradually within 2 to 4 weeks. This recovery may go no further than the unresponsiveness wakefulness syndrome or the minimally conscious state, or these may be stages (brief or prolonged) on the way to more complete recovery of consciousness. The prognosis of coma survivors following brain anoxia is worse than following trauma. In anoxic coma, absent or stereotyped motor responses and absent pupillary reflexes indicate bad outcome. Paraclinically, isoelectrical ("flat") or "burst-suppression" electroencephalography (EEG) and the bilateral absence of somatosensory evoked potentials (in primary cortex (called N20 wave or potential) are strong indicators of bad outcome. In contrast, auditory oddball evoked potentials showing an intact mismatch negativity effect forebodes an outcome better than death or unresponsive wakefulness.

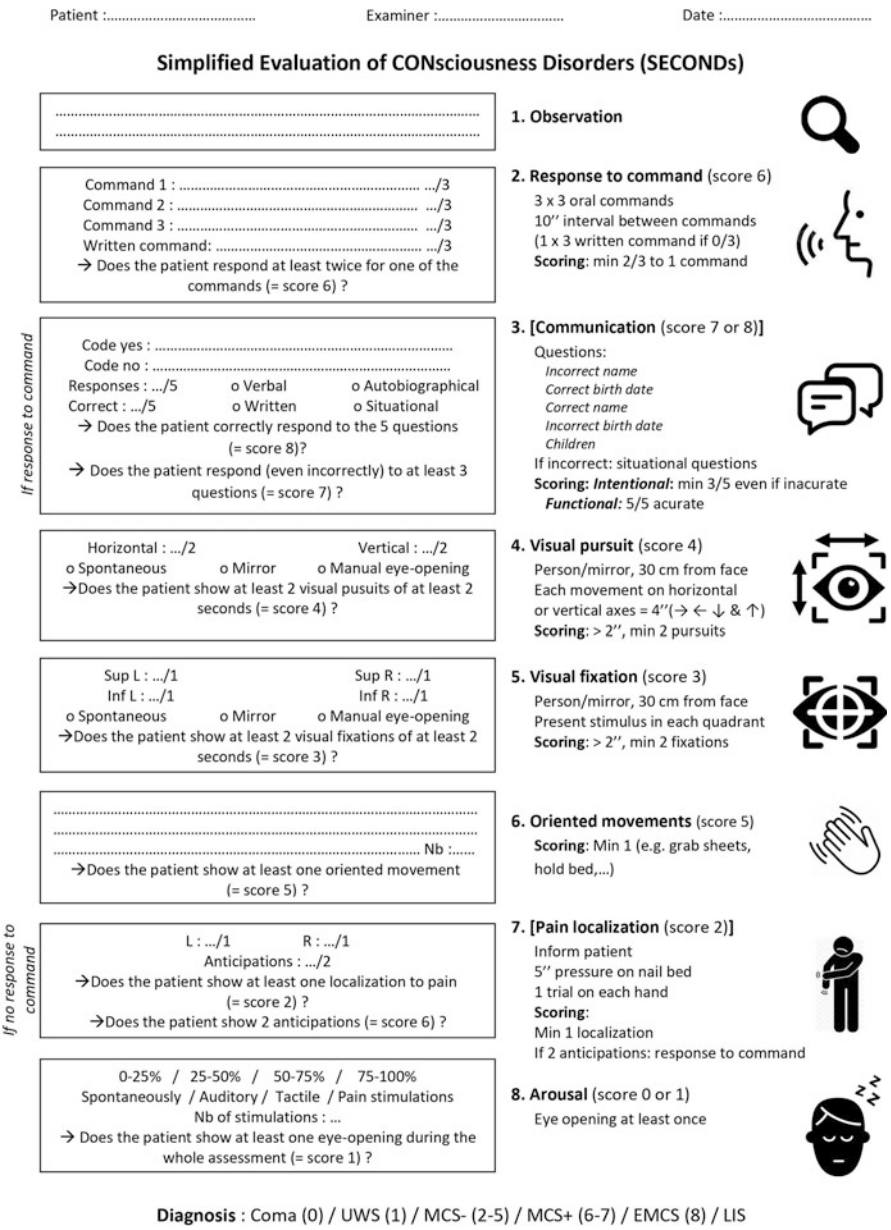

Fig. 3 The Simplified Evaluation of CONsciousness Disorders (SECONDs) scale to diagnose patients with disorders of consciousness. (Taken from Sanz et al., J Vis Exp. 2021)

Positron emission tomography (PET) studies show that, on average, grey matter metabolism is 50–70% of normal values in comatose patients of traumatic or hypoxic origin. A global depression of cerebral metabolism is not unique to coma.

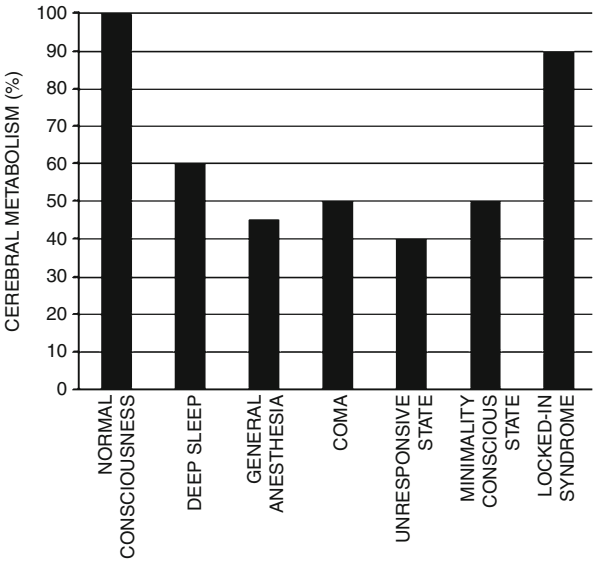

Fig. 4 Overall cortical metabolism in coma, unresponsive wakefulness syndrome, minimally conscious and locked-in syndromes as compared to slow wave sleep, and anesthesia

When different anesthetics are titrated to the point of unresponsiveness, the resulting reduction in brain metabolism is similar as that observed in comatose patients. Another example of transient metabolic depression can be observed during deep sleep (stage III). In this daily physiological condition, cortical cerebral metabolism can drop to nearly 40% of normal values (Fig. 4).

Brain Death and "Clinical" Death

The widespread use of the artificial respirator in the 1960s led to the redefinition of death based on neurological criteria (i.e., brain death or irreversible coma with absent brainstem reflexes). Brain death means human death determined by neurological criteria. It is an unfortunate term as it misleadingly suggests that there are two types of death: brain death and "regular" death. There is, however, only one type of death which can be measured in two ways: by cardiorespiratory and by neurological criteria. The currently most accepted definition of death is the permanent cessation of the critical functions (i.e., respiration, circulation, and consciousness) of the organism as a whole.

Brain death results from irreversible loss of brain and brainstem function and is classically caused by a brain lesion (e.g., massive traumatic injury, intracranial hemorrhage, or anoxia) which increases intracranial pressure to values superior to mean arterial blood pressure and hence causes intracranial circulation to cease and damage the brainstem due to herniation. Anatomopathology in brain death patients receiving maximal artificial means of support will inevitably end up showing the so-called respirator brain: surface vasocongestion due to venous engorgement,

Table 1 Diagnostic criteria for brain death as published by the American Academy of Neurology

Demonstration of coma.
Evidence for the cause of coma.
Absence of confounding factors, including hypothermia, drugs, electrolyte, and endocrine disturbances.
Absence of brainstem reflexes.
Absent motor responses
Apnea.
A repeat evaluation in 6 h is advised, but the time period is considered arbitrary.
Confirmatory laboratory tests are only required when specific components of the clinical testing cannot be reliably evaluated.

thrombosis in cortical veins and sinuses, subarachnoid hemorrhage, and cortical congestion and hemorrhage will be observed after about 12 h of a non-perfused state. After about a week an autolyzed liquefied brain will pour from the opened skull.

The concept of brain death as defining the death of the individual is largely accepted. Most countries have published recommendations for the diagnosis of brain death, but the diagnostic criteria differ from country to country. Some rely on the death of the brainstem only; others require death of the whole brain including the brainstem. However, the clinical assessments for brain death are very uniform and based on the irreversible loss of all brainstem reflexes and the demonstration of continuing apnea in a persistently comatose patient. Table 1 shows the clinical criteria for brain death as defined by the American Academy of Neurology – including the very important apnea testing – which have been used to model many institutional policies. Since the first definition of the neurologic criteria of death over 45 years ago, no patient in apneic coma properly declared brain (or brainstem) death has ever regained consciousness.

It is important to stress that *clinical death* is a term to be avoided, referring in popular media to cessation of blood circulation and breathing. Under the US Uniform Determination of Death Act, a person is dead when physicians determine, by applying prevailing clinical criteria, that cardiorespiratory or brain functions are absent and cannot be retrieved. This notion of irreversibility is reflected in the "Pittsburgh protocol" for organ "donation after cardiac death." Here, patients who are hopelessly brain-damaged (but not brain dead) can have their life-sustaining therapy (i.e., positive-pressure ventilation) withdrawn. Once their heart stops beating for a period of 3–10 min (that varies by protocol), they can be declared dead (and only then can be organs procured).

Defining death and organ harvesting are inextricably linked because of the "dead donor rule." This rule requires patients to be declared dead before the removal of life-sustaining organs for transplantation. Some authors have proposed that death be defined by the permanent cessation of the higher functions of the nervous system that demarcate man from the lower primates. This neocortical or higher brain death definition has been mainly developed by philosophers, and its conceptual basis rests on the premise that consciousness, cognition, and social interaction, not the

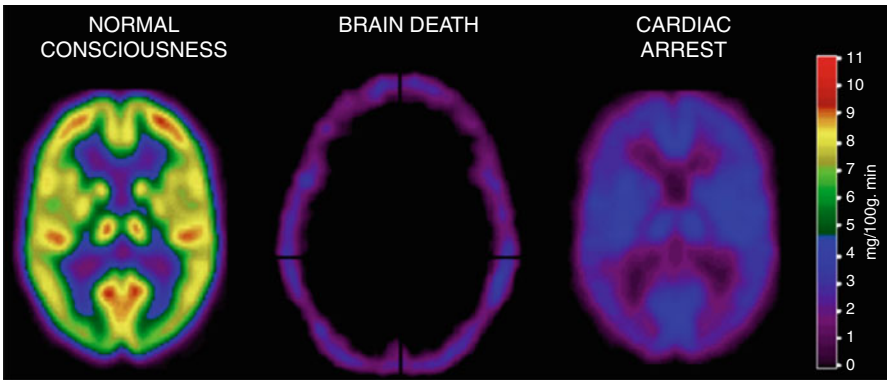

Fig. 5 Positron emission tomography (PET) scans illustrating the "empty skull sign" in brain death and massive global decrease of brain metabolism in a cardiac arrest survivor. The color scale shows the amount of glucose metabolized per 100 g of brain tissue per minute

bodily physiological integrity, are the essential characteristics of human life. Based on this definition, unresponsive patients following an acute injury or chronic degenerative disease and anencephalic infants are considered dead. The neocortical definition of death has never convinced medical associations or courts.

Cerebral angiography and transcranial Doppler sonography can be used with very high sensitivity and 100% specificity to document the absence of cerebral blood flow in brain death. Similarly, radionuclide cerebral imaging such as single-photon emission CT and PET classically shows the so-called hollow skull sign confirming the absence of neuronal function in the whole brain (see Fig. 5). The EEG in brain death shows absent electrocortical activity (i.e., isoelectric or "flat" recording) with a sensitivity and specificity of 90%. It is the most validated and, because of its wide availability, preferred confirmatory test for brain death implemented in many countries' guidelines.

"Near" Death

Near-death experiences (NDE) and out-of-body experiences remain fascinating phenomena, which are abundant in popular beliefs, mythology, and spiritual experiences of many ancient and modern societies. At present, there exists no universally accepted definition of NDE. Given that, there are many ways of categorizing its phenomenological elements. Common NDE features are ineffability, seeing a dark tunnel, experiencing a bright light as a "being of light," meeting "spiritual beings," being "out of the body," coming back "into the body," feelings of peace and quiet, panoramic life review, experiencing a realm in which all knowledge exists, and sensing a border or limit.

Clinical studies suggest that characteristics of NDE are a culturally invariant physiological reality that can be investigated scientifically. The scale most

commonly used to quantify these subjective experiences is the "NDE Greyson Scale," consisting of 16 questions. In order to consider the subjective report as being a true NDE, a minimum score of 7 on 32 needs to be obtained. Recently, an updated scale was developed, the Near-Death Experience Content (NDE-C) scale, which allows quantifying NDE in a more complete way, as it is based on the NDE Greyson Scale and on the most recent empirical evidence. This new 20-item scale is a psychometrically sound self-report instrument for assessing NDE, which should facilitate future research.

What causes NDE? They seem to occur in a minority of individuals close to death (after both traumatic and nontraumatic coma) or in situations of intense physical or emotional danger. Besides these "classical" NDE, other individuals have reported similar experiences during non-life-threatening situations such as during sleep, meditation, or even spontaneously, and these are referred to as NDE-like. Early NDE studies have focused on cardiac arrest survivors. Spiritual interpretations consider their existence as evidence that the mind (i.e., spirit or soul) can be separated from the physical body. Supporters of this theory consider that NDE provide a glimpse of the spiritual realm to which the soul migrates after death. The second category encompasses psychological explanations according to which NDE are a type of depersonalization acting as a protection against the threat of death in situations of intense danger, by allowing an engagement in pleasurable fantasies. Others proposed a concept of psychological absorption, which may be defined as the tendency to focus attention on imaginative or selected sensory experiences to the exclusion of stimuli from the external environment. We will here focus on so-called organic hypotheses, accounting for components of NDE in terms of brain dysfunctions and alterations.

Prospective studies of cardiac arrest patients show that about 10% report memories or NDE of their period of "coma" or unconsciousness. Most patients reported these to be pleasant, but around 15% of NDE experiencers (including cardiac arrest and other causes) report negative experiences that can be categorized into inverse, hellish, and void experiences. These distressing NDE are more often associated with suicidal attempts.

Due to the small number of patients studied after cardiac arrest, it is not possible to draw any clear conclusions regarding possible causative physiological factors such as administered drugs, duration of cardiac arrest or dysrhythmia, hypoxia, hypercarbia, or electrolyte disturbances around the period of arrest. These experiences often produce long-lasting effects in terms of increase in belief in an afterlife and decreased fear of death, increase interest in the meaning of one's own life, and increased social awareness such as showing love and accepting others. Memories of NDE are unique because they are associated with a particularly rich amount of phenomenological characteristics. They are often reported as more real than a dream or the imagination of a past biographical event. Moreover, the memory trace of a NDE does not fade with time and is often reported as a self-defining memory by the experiencers. Additionally, certain psychological mechanisms (e.g., false memory susceptibility) and personality traits (e.g., fantasy proneness) correlate with the emergence and the richness of such experiences.

Anoxic or traumatic brain damage leads to a complex neurometabolic cascade with the release of multiple neurotransmitters which, combined with administered centrally acting drugs during resuscitation or intensive care, may produce such effects as analgesia, euphoria, and detachment. These effects combined with regional hypoxic neuronal dysfunction may produce epileptiform discharges, possibly leading to the reported phenomenology of NDE. There exists no EEG data about brain function in the critical clinical period that is assumed to be associated with NDE. Indeed, in all peer-reviewed studies, loss of consciousness was "diagnosed" only by electrocardiogram examinations, independently of neurological records. However, in recent years, the neurophysiological mechanisms underlying subjective laboratory-induced experiences that closely resemble classical NDE have been investigated through different techniques, such as hypnosis (by reexperiencing a previous NDE), syncope (using hyperventilation, orthostasis, and the valsalva maneuver), or psychedelic intake such as ketamine or psilocybin. To a certain degree, reproducing NDE-like in laboratory settings permits to go beyond previous limitations inherent in such particular research (e.g., the lack of real-time brain monitoring) and to test the current neurobiological hypotheses by objectively mapping brain changes.

One of the principal components of NDE is the out-of-body experience, defined by the presence of (i) disembodiment (i.e., location of the self outside one's body), (ii) the impression of seeing the world from an elevated and distanced visuospatial perspective, and (iii) the impression of seeing one's own body from this perspective (i.e., autoscopy). There is increasing evidence showing that out-of-body experiences may result from a deficient multisensory integration at the right temporoparietal junction area. Focal electrical stimulation of this area induced repeated out-of-body experiences (Fig. 6). In studies of neurological patients suffering from epilepsy-related "out-of-body experiences," lesion overlap was centered on the right temporoparietal junction. Altered spatial self-recognition seems mediated by this area that is known to be involved in vestibular-somatosensory integration of body orientation in space.

Using electrophysiology, transient electrical spikes have been observed in critically ill patients immediately before cardiac arrest as well as transient and global surge of synchronized gamma oscillations during cardiac arrests in rats. These observations lead to the hypothesis that NDE could be caused by transient organized brain activity and neurophysiologic states at near death. Other scientists posit that NDE may be associated with the release of endogenous neurotransmitters, particularly highlighting dysregulated serotonergic activity and massive liberation of endorphins. It is however likely that several neurophysiological factors trigger a NDE (Fig. 6). Similarly, based on knowledge from functional neuroimaging and clinical neurological studies, it can be hypothesized that the other distinctive dimensions of NDE can be related to particular regional brain dysfunction: (i) occipital and optic radiation area lesions could account for tunnel and light vision, (ii) mesiotemporal areas (encompassing amygdala and hippocampus) for life review, memory flashback and enhanced emotions, (iii) left temporoparietal junction areas for the meeting of spirits, (iv) anterior cingulate areas for the state of painlessness and well-being,

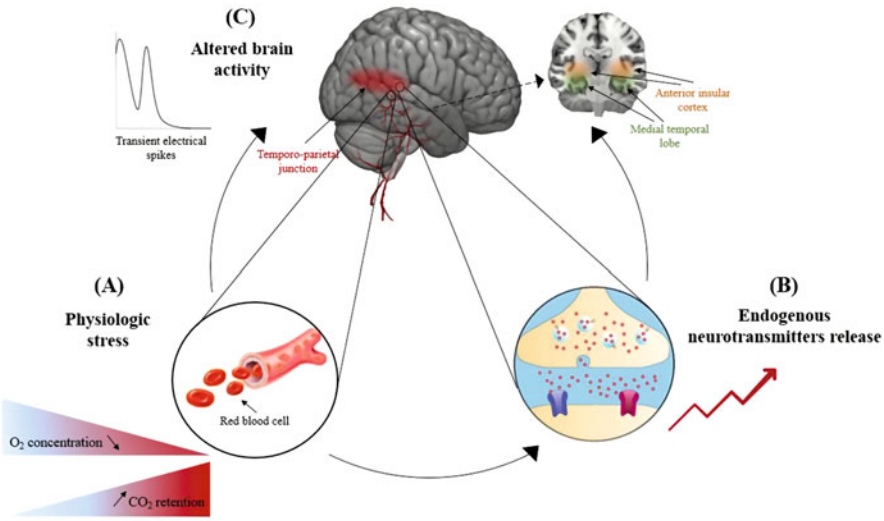

Fig. 6 Neurophysiological mechanisms potentially involved in the emergence of NDE and NDE-like. (**a**) physiologic stress including disturbed levels of blood gases, such as transient decrease cerebral oxygen (O2) levels and elevated carbon dioxide (CO2) levels and, probably occurred as a secondary change, (**b**) naturally occurring release of endogenous neurotransmitters including endogenous N-methyl-D-aspartate (NMDA) antagonists and endorphins. Both (**a**) and (**b**) may contribute to (**c**) dysfunctions of the medial temporal lobe, the temporoparietal junction (know to induce out-of-body experience when electrically stimulated), and the anterior insular cortex. A NDE may result from these neurophysiological processes, or their interactions, but the exact causal relationship is still undetermined

(v) cortico-striatal networks for time distortion, and (vi) biparietal posterior cortices for transcendental oneness, cosmic unity, and mystical experiences. But further studies are awaited to better document the functional neuroanatomy of the complex subjectivity of NDE. In the meantime and based on recent empirical literature, a new theoretical framework has been proposed to better study NDE and other modified states of consciousness, notably by including the concepts of responsiveness and (dis)connectedness.

Locked-in Syndrome

The locked-in syndrome describes patients who are awake and conscious but have no means of producing speech, limb, or face movements (Table 2). The syndrome can be categorized on the basis of the extent of motor impairment: (a) *classical* locked-in syndrome is characterized by total immobility except for vertical eye movements or blinking; (b) *incomplete* locked-in syndrome permits remnants of voluntary motion such as moving a finger or the head; and (c) *total* (or *complete*) locked-in syndrome consists of complete immobility including all eye movements

Table 2 Diagnostic criteria for locked-in syndrome as published by the American Congress of Rehabilitation Medicine

The presence of sustained eye-opening (bilateral ptosis should be ruled out as a complicating factor).
Preserved basic cognitive abilities.
Aphonia or severe hypophonia.
Quadriplegia or quadriparesis.
A primary mode of communication that uses vertical or lateral eye movement or blinking of the upper eyelid.

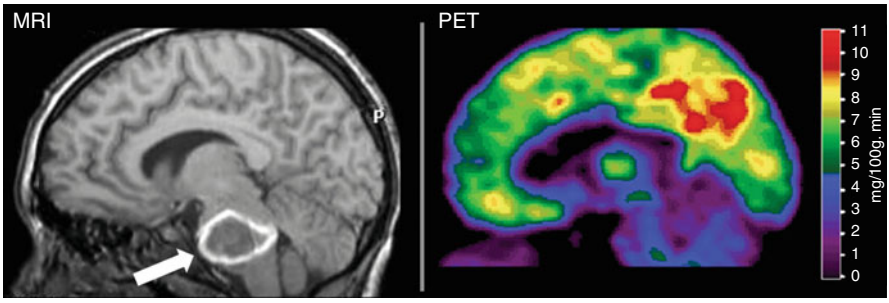

Fig. 7 Left: Magnetic resonance image (MRI) showing a massive hemorrhage in the brainstem (arrow) causing a complete locked-in syndrome in a 13-year-old girl. Right: positron emission tomography (PET) scan illustrating intact brain function. The color scale shows the amount of glucose metabolized per 100 g of brain tissue per minute

combined with preserved consciousness. The cause is most frequently a ventral pontine lesion of the brainstem due to stroke or hemorrhage (but traumatic and other causes can also be encountered) (Fig. 7).

The term was first introduced to medicine in the 1960s, but the earliest example of a "locked-in" patient comes from Alexandre Dumas's novel the Count of Monte Cristo (1844). Herein a character, Monsieur Noirtier de Villefort, was depicted as "a corpse with living eyes." For more than 6 years, a helper pointed at words in a dictionary and Mr. Noirtier indicated with his eyes the words he wanted. Some years later, Emile Zola wrote in his novel Thérèse Raquin (1868) about a paralyzed woman who "was buried alive in a dead body" and "had language only in her eyes." Dumas and Zola highlighted the locked-in condition before the medical community did. In 1995, Frenchmen Jean-Dominique Bauby, aged 43 and editor in chief of the fashion magazine "Elle," had a brainstem stroke. He emerged from a coma several weeks later to find himself in a locked-in syndrome only able to move his left eyelid. Bauby wanted to show the world that this disease, which impedes movement and speech, does not prevent patients from living. He has proven it in an extraordinary book in which he composed each passage mentally and then dictated it, letter by letter, to an assistant who painstakingly recited a frequency-ordered alphabet until Bauby chose a letter by blinking his eye once to signify "yes." His book *The Diving Bell and the Butterfly* became a best seller only weeks after his death due to infection in 1997 and

had been turned into a movie in 2007. Bauby created an Association for Locked-In Syndrome (www.alis-asso.fr) aimed to help patients with this condition and their families. Since its creation, they have registered over 890 locked-in patients, and they are currently following 350 of them in France and surroundings.

Unless the physician is familiar with the signs and symptoms of the locked-in syndrome, the diagnosis may be missed, and the patient may erroneously be considered as being unconscious. Classically, structural brain imaging (X-ray CT or MRI) shows isolated lesions of the brainstem that should caution the physician. However, studies have shown that in up to half of the cases, the first to realize the patient was conscious was the family and not the medical team. Most distressingly, the time elapsed between the brain insult and the diagnosis on average seems 2 months. The presence of a relatively normal and reactive electroencephalographic (EEG) rhythm in a patient that appears to be unconscious should alert to the diagnosis, but abnormal and unreactive EEG patterns can also be observed. So-called "active" cognitive event-related potentials have shown their utility to document consciousness in total locked-in syndrome. Figure 8 illustrates this method in a 21-year-old woman who failed to show any motor sign of consciousness

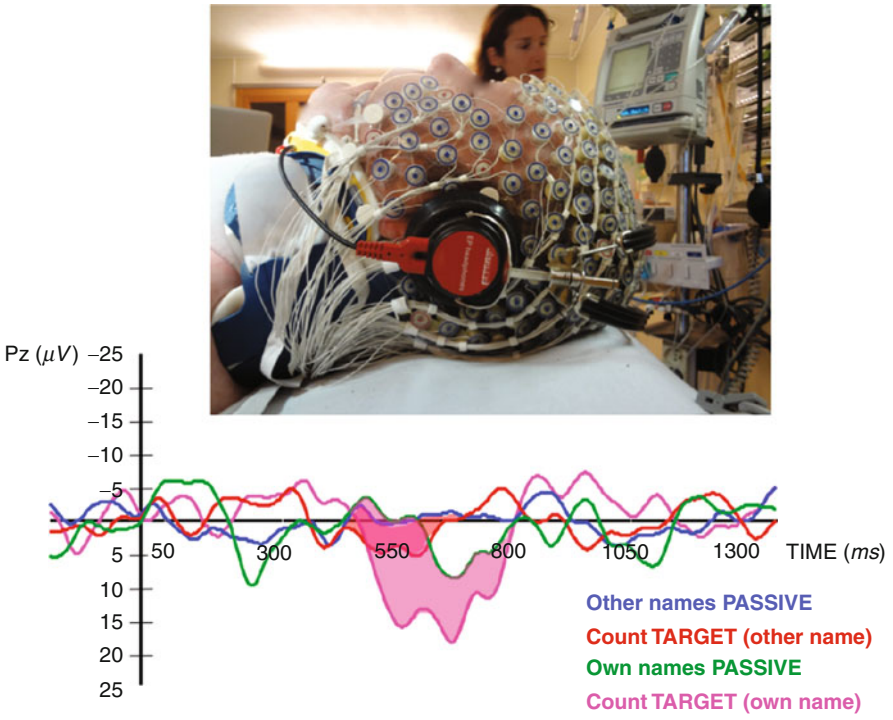

Fig 8 "*Active*" event-related potentials showing command-following ("count a name") and hence *total* locked-in syndrome. The increase in amplitude of the "P3 wave" (shown in pink) demonstrates that the clinically comatose patient understood and performed the task and therefore must be conscious.

up to 49 days after a basilar artery thrombosis. The patient was presented sequences of names containing the patient's own name and other names and was instructed to count her own name or to count another target name. A specific P3 wave could be recorded for the voluntarily counted names only, demonstrating the presence of command-following and hence of consciousness. Two weeks later the patient recovered some clinical signs of consciousness and later could communicate using a computer controlled by small finger movements. This specific paradigm has since been used in many other studies to detect cover consciousness in patients with disorders of consciousness.

PET scanning has shown significantly higher global brain metabolism in the brains of patients in a locked-in syndrome compared to patients in coma or with unresponsive wakefulness syndrome. No cortical area showed lower metabolism in acute and chronic locked-in syndrome patients when compared to age-matched healthy controls (Fig. 7). Conversely, a hyperactivity was observed in bilateral amygdala of acute, but not chronic, locked-in syndrome patients. The absence of metabolic signs of reduced function in any area of the gray matter re-emphasizes the fact that locked-in syndrome patients suffer from a pure motor de-efferentation and recover an entirely intact intellectual capacity. Amygdala activation is known to be related to negative emotions such as fear and anxiety. It is difficult to make judgments about patient's thoughts and feelings when they awake from their coma in a motionless shell. However, it can be assumed that the increased activity in the amygdala, in the absence of decreased neural activity in any cortical region, relates to the terrifying situation of an intact awareness in a sensitive being, experiencing stress, anguish, and frustration, locked in an immobile body. Healthcare workers should adapt their bedside behavior and consider pharmacological anxiolytic therapy of locked-in patients, taking into account the intense emotional state they go through.

To allow measurements of intellectual functions in classical locked-in syndrome, adapted neuropsychological testing batteries based on eye-coded communication have been developed. In cases of pure brainstem lesions, patients will recover intact cognition, but additional cortical injuries can lead to associated cognitive deficits. For those not dealing with these patients on a daily basis, it is surprising to see how chronic locked-in syndrome patients, with the help of family and friends, can have essential social interaction and lead meaningful lives.

In the acute phase, mortality is high, but after the intensive care period, and given appropriate medical and nursing care, life expectancy can be many decades. Despite the classically encountered persisting serious motor deficit, most patients do recover some distal control of fingers and toe movements, sometimes allowing a functional use of a digital switch. The vast majority of patients remain dependent of others for activities of daily living. Given appropriate rehabilitation, most will recover some head or limb movement (although remaining wheelchair-bound), and about half will be able to eat without gastrostomy, breath without tracheotomy, and recover some speech production (although limited to single comprehensible words).

Current eye-controlled computer-based communication technology is changing the lives of patients with locked-in syndrome (see video for example). Instead of passively responding to the requests of others, this technology allows patients to

control their environment (lights, appliances, etc.), initiate conversations using a word processor, or access the Internet. Unfortunately the cost of these devices is substantial and not routinely paid for by third parties. The preeminent physicist Stephen Hawking, author of *A Brief History of Time*, almost completely paralyzed due motor neuron disease until he passed away in 2018, communicated using one finger and a computerized voice synthesizer. His continuing brilliant productivity despite the failure to move or speak illustrates that locked-in patients can be productive members of the society.

Video LIS
A locked-in person moves a cursor on screen by eye movements. An infrared camera mounted below the monitor observes one of the user's eyes; an image processing software continually analyzes the video image of the eye and determines where he is looking on the screen. The patient looks at a virtual keyboard that is displayed on the monitor and uses his eye as a computer-mouse. To "click" he looks at the key for a specified period of time (typically a fraction of a second) or blinks. An array of menu keys allow the user to control his environment, use a speech synthesizer, browse the world wide web, or send electronic mail independently (video used with kind permission from the patient).

Unresponsive Wakefulness Syndrome

In the 1970s patients who awakened from coma (meaning they open their eyes spontaneously or after stimulation) but remained without communication or behavioral sign of consciousness were coined to be in a "vegetative state" (previously called "apallic syndrome" or "coma vigil") (Table 3). "Vegetative" was chosen to refer to the preserved vegetative (autonomous) nervous functioning in these patients (e.g., sleep-wake rhythm, respiration, digestion, and thermoregulation). The term "persistent" was added to denote that the condition remained for more than 1 month after insult. In 1994, a retrospective study of all published cases permitted to propose temporal boundaries for irreversibility of this syndrome, hence proposing the term "permanent vegetative state" (unfortunately *persistent* and *permanent* vegetative

Table 3 Diagnostic criteria for the "vegetative" state as published by the US Multi-Society Task Force

No evidence of awareness of self or environment and an inability to interact with others
No evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli
No evidence of language comprehension or expression
Intermittent wakefulness manifested by the presence of sleep-wake cycles
Sufficiently preserved hypothalamic and brainstem autonomic functions to permit survival with medical and nursing care
Bowel and bladder incontinence
Variably preserved cranial nerve and spinal reflexes

state share the common abbreviation of "PVS" leading to unwarranted confusion). It is to these cases that end-of-life issues of withholding and withdrawal of life-sustaining treatment (i.e., artificial hydration and nutrition) are related, as we will discuss later on.

Over the last four decades, some clinicians felt uncomfortable when referring to patients as "vegetative." Therefore the term "unresponsive wakefulness syndrome" was proposed in 2010 as a more neutral and descriptive term. The reasons for referring to these patients as "unresponsive" rather than "vegetative" are multiple. The word vegetative has an unintended albeit persistent negative connotation. The Oxford English dictionary defines "vegetative" as "an organic body capable of growth and development but devoid of sensation and thought" and "to vegetate" as to "live a merely physical life devoid of intellectual activity or social intercourse." The notion of a vegetative nervous system dates to the 1800s when the nervous system was divided into animalic (i.e., related to sensory perception and voluntary motor responses) and vegetative parts (i.e., assuring nutritional functions). Unfortunately, for many laypersons it has a pejorative undertone and may incorrectly refer to these patients as being "vegetable-like."

Some books written by patients erroneously considered as "vegetative" illustrate this point. A striking example is *Look up for Yes* written by Julia Tavalaro (1997) who had a subarachnoid hemorrhage when 32 years old. She remained in a coma for 7 months and gradually woke up to find herself in a New York State chronic care facility. There, she was known as *the vegetable*, and it was not until 6 years later that her family identified a voluntary "attempt to smile." Later, using a letter board, she related the turmoil of her terrible years in captivity and could cheek-control her wheelchair around the hospital. Another poignant testimony is *Only the Eyes Say Yes* (1997) by Philippe Vigand. He had a vertebral artery dissection when 32 years old and remained in a coma for 2 months. He and his wife write that at first, doctors believed he was *a vegetable and was treated as such*. His wife eventually realized that he was voluntarily blinking his eyes but had difficulties convincing the treating physicians. After many months of hospital care, he was brought home where an infrared camera attached to a computer enabled him to write his book. Both Julia Tavalaro and Philippe Vigand were thus misdiagnosed while they should have been early on diagnosed with a locked-in syndrome.

In addition, "vegetative state" for many physicians implies "cortical death" and persistency from the moment of diagnosis. This already started when the New York Times (August 5, 1968) announced the Harvard criteria for brain death. In the accompanying editorial it read: "As old as medicine is the question of what to do about the human vegetable... Sometimes these living corpses have survived for years... It is such cases, as well as the need for organs to be transplanted that the Harvard faculty committee had in mind in urging that death be redefined as irreversible coma." The case of Terri Schiavo also illustrates this point, as commentators have inaccurately referred to her condition as "brain death" or "neocortical death."

In the "vegetative" state, the brainstem is relatively spared, whereas the grey and white matters of both cerebral hemispheres are widely and severely damaged. Overall cortical metabolism of these patients is 40–50% of normal values.

Characteristic is a relative sparing of metabolism in the brainstem "activating reticular formation," hypothalamus, and basal forebrain. The functional preservation of these structures allows for their preserved arousal and autonomic functions. The other hallmark is a systematic impairment of metabolism in the polymodal associative cortices (bilateral prefrontal regions, Broca's area, parietotemporal and posterior parietal areas, and precuneus). These regions are known to be important in various functions such as attention, memory, and language. It has long been controversial whether the observed metabolic impairment in this large frontoparietal cortical network reflects an irreversible structural neuronal loss, or functional and potentially reversible damage. However, when unresponsive patients recover awareness, PET shows a functional recovery of metabolism in these same cortical regions. Moreover, the resumption of long-range functional connectivity between these associative cortices and between some of these and the intralaminar thalamic nuclei parallels the restoration of their functional integrity. The cellular mechanisms which underlie this functional normalization remain putative: axonal sprouting, neurite outgrowth, and cell division (known to occur predominantly in associative cortices in normal primates) have been proposed candidate processes. The challenge is now to identify the conditions in which, and the mechanisms by which, some unresponsive patients may recover consciousness.

Patients with disorders of consciousness are not uniformly hopeless, and increasing evidence from clinical and neuroimaging studies has shown that clinicians need to be cautious about making strong claims concerning allegedly "vegetative" patients' consciousness. Clinical practice shows that once stamped with the diagnosis of "vegetative state," it is frequently difficult to change the label, and the first signs of recovery of consciousness are too often missed. Terry Wallis, who made the headlines when starting to speak after being considered as "vegetative" for 19 years post-trauma, well illustrates this point. Subsequent analysis of his medical files showed he actually was minimally conscious for all those years (albeit lacking proper rehabilitation).

Minimally Conscious State

Some unresponsive patients will irreversibly remain in this condition, but many may evolve to a minimally conscious state (MCS). Table 4 summarizes its operational criteria, separating noncommunicative unresponsive patients from noncommunicative patients showing minimal behavioral signs of consciousness. Emergence from the minimally conscious state was defined by functional communication or functional use of objects. Since its formal definition in 2002, a number of authors have questioned the usefulness of differentiating unresponsive from minimally conscious patients considering both patient groups as hopelessly brain-damaged.

Recent studies have demonstrated it is important to disentangle both clinical entities as functional neuroimaging have shown differences in residual cerebral processing and, hence, conscious perception, as well as differences in outcome. However, controlled prospective studies on prognosis (and on treatment) in large,

Table 4 Diagnostic criteria for the minimally conscious state as published by the American Academy of Neurology

Presence of limited but clearly discernible evidence of consciousness of self or environment, on a reproducible or sustained basis, by at least one of the following behaviors:
Following simple commands
Gestural or verbal yes/no response (regardless of accuracy)
Intelligible verbalization
Purposeful behavior (including movements or affective behavior that occur in contingent relation to relevant environment stimuli and are not due to reflexive activity)
The emergence of MCS is defined by:
Ability to use functional interactive communication
Functional use of objects

well-described cohorts of patients with disorders of consciousness, permitting evidence-based decision-making, are still awaited. The World Health Organization now recognizes MCS in its International Statistical Classification of Diseases. ICD codes classify symptoms, diseases, or injuries into categories with unique codes permitting standardized epidemiological, morbidity, and mortality studies and reimbursement and medical decision-making.

"Akinetic mutism" is an outdated term that should better be avoided and is now considered to be a subcategory of the minimally conscious state. It was first introduced in 1941 to describe a condition characterized by severe poverty of movement, speech, and thought without associated arousal disorder or descending motor tract impairment. Typical for akinetic mutism is the complete or near-complete loss of spontaneity and initiation so that action, ideation, speech, and emotion are uniformly reduced. The absence of internally guided behavior allows attention to be passively drawn to any environmental stimulus that the patient is exposed to. The preservation of spontaneous visual tracking and occasional, albeit infrequent, speech and movement to command help differentiate akinetic mutism from the unresponsive state.

In 2011, the clinically heterogeneous "MCS entity" was subcategorized in minimally conscious PLUS (MCS+) and MINUS (MCS-) based on the presence of absence of language-related responses. MCS+ was defined by the presence of (i) command-following, (ii) intelligible verbalization, or (iii) gestural or verbal yes/no responses. In contrast, MCS- patients only show non-related language behavioral interaction characterized by the presence of non-reflex movements such as (i) orientation of noxious stimuli, (ii) pursuit eye movements that occur in direct response to moving or salient stimuli, (iii) movements or affective behaviors that occur in contingent relation to relevant environmental stimuli (such as reaching for objects that demonstrates a clear relationship between object location and direction of reach, touching or holding objects in a manner that accommodates the size and shape of the object, appropriate smiling or crying in response to the visual content of emotional but not to neutral topics or stimuli). Besides these behaviors, other non-related language responses have recently been proposed as new signs of

consciousness, such as resistance to manual eye-opening, efficacy of the oral phase of swallowing, responses to olfaction stimuli, or habituation of the auditory reflex.

Recent neuroimaging studies have shown differences between MCS+ and MCS- patients. Notably, MCS+ patients showed a higher brain metabolism in the left middle temporal cortex, which is known to be important for semantic processing. Moreover, the reappearance of language-related behaviors seems to parallel the recovery of metabolism and grey matter in neural regions that are associated with self-consciousness and language processing. Outcome studies also show a better prognosis for MCS+ compared to MCS- patients.

In patients in minimally conscious state, the overall cerebral metabolism is decreased compared to healthy subjects but higher than the one in the unresponsive state. Metabolic activity in the frontoparietal network allows to differentiate minimally conscious from unresponsive patients. This network is considered critical in awareness, as will be discussed in the next section. It includes the medial parietal cortex (precuneus) and adjacent posterior cingulate, which are among the most active brain regions in conscious waking and among the least active regions in altered states of consciousness, such as general anesthesia, sleep, hypnotic state, dementia and Wernicke-Korsakoff's or postanoxic amnesia. It has been suggested that this richly connected multimodal posteromedial associative area is a critical hub in the neural network subserving human *internal* awareness (Fig. 9). Simple auditory stimulation has been shown to induce a more widespread activation in minimally conscious than in unresponsive patients. In the former, activation encompassed not only primary but also higher-order associative areas, suggesting a more elaborate level of processing. Moreover, cortico-cortical functional connectivity is more efficient in the minimally conscious state, compared to the unresponsive, between auditory cortex and the frontoparietal network. Such findings encourage ongoing developments of neuromodulatory and cognitive revalidation therapeutic strategies in minimally conscious patients.

In response to natural language stimuli (e.g., meaningful sentences), fMRI activation patterns of minimally conscious patients exhibiting command-following were examined by Schiff et al. during presentation of forward and backward narratives read in a familiar voice and containing personally meaningful content. Components of the cortical language networks showed selective activation compared to baseline conditions. Presentation of the narratives time-reversed (played backward) that shared most of the physical properties of the sounds activated the same networks as forward narratives in the normal controls subject but failed to activate the networks in the minimally conscious patients. These findings correlate with low resting metabolic activity and suggest that a residual capacity to activate large integrative networks may remain in some minimally conscious patients. Preservation of large-scale networks in these patients may underlie late recoveries of verbal fluency in such patients.

It is important to stress that the clinical diagnosis of these patients' (minimal) consciousness is based on the assessment of motor responsiveness. As will be discussed at the end of this chapter, functional neuroimaging (e.g., PET and functional MRI) and cognitive evoked potential studies have offered the possibility to

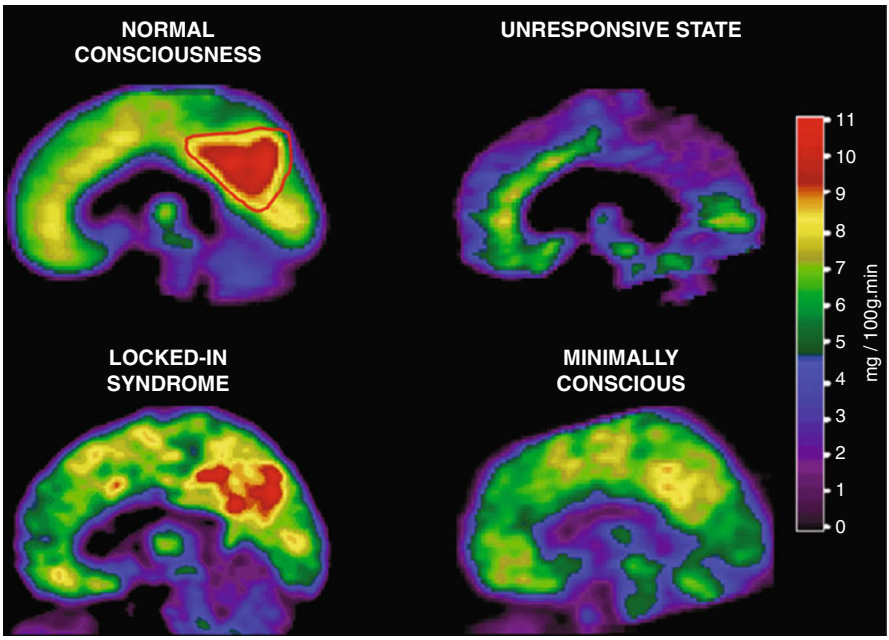

Fig. 9 In normal conscious waking, the medial posterior cortex (encompassing the precuneus and adjacent posterior cingulate cortex, delineated by a red line) is the metabolically most active region of the brain; in unresponsive patients, this same area (delineated by a blue line) is the metabolically least active region. In the locked-in syndrome, no supratentorial brain region shows significant decreases in metabolism. In the minimally conscious state, the precuneus and posterior cingulate cortex shows an intermediate metabolism, higher than in unresponsive patients, but lower than in conscious controls

measure directly and noninvasively severely brain-damaged patients' brain activity at rest and during external activation. More recently, these techniques have been further developed aiming to detect "neural" (motor-independent) proof of command-following and communication. Using fMRI, it was shown that some clinically unresponsive patients could perform mental imagery tasks. When these patients were asked to imagine performing sport (e.g., tennis), robust activation could be recorded in motor areas. Other instructions such as "imagine moving around in your house" resulted in activation elsewhere in the brain (i.e., parahippocampal activation for spatial navigation tasks). These specific activations patterns were not different from those observed in healthy volunteers.

In a next step, scientists have employed this technique to establish fMRI-based communication. Here, patients are asked to answer autobiographical questions by doing motor imagery to answer "yes" and mental spatial navigation to answer "no" (Fig. 10). Note that many (minimally conscious) patients or classical locked-in patients fail to show reliable fMRI communication, illustrating the major limitations regarding the sensitivity of these techniques. Concurrently, cheaper and portable techniques using event-related potential or electromyography "active" paradigms

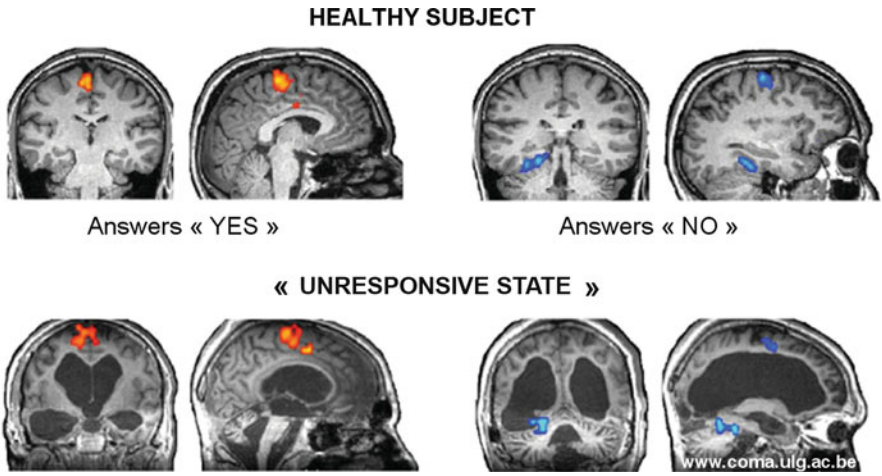

Fig. 10 Reliable fMRI-based communication in severely brain-damaged patients unable to show any motor pathway-dependent communication. To answer "yes" a motor imagery task, activating motor areas (in orange), is performed. To answer "no" a spatial navigation task, activating another set of areas encompassing the parahippocampal regions (in blue), is performed

have been developed to detect possible signs of command-following not assessable by clinical behavioral examination. These fMRI and EEG active paradigms are now more commonly used (with also other commands) in both the acute and chronic settings. A recent meta-analysis reported that around 15% of unresponsive patients are actually able to follow commands by modifying their brain activity with such paradigms.

The medical community has yet not come up with a specific diagnostic category for these patients showing only signs of consciousness or communication on paraclinical fMRI or evoked potential studies. In the presence of increasingly "hard" neurophysiologic markers of consciousness, the burden of proof for establishing consciousness in severely brain-damaged patients no longer exclusively lies in behavioral assessment. Clearly, patients who can "play tennis" and "imagine walking in their house" or use these complex mental imagery tasks to accurately communicate cannot be considered unresponsive or minimally conscious. Some have proposed to call this condition "functional locked-in syndrome," while others have suggested the term "cognitive-motor dissociation," "cover awareness," or MCS*. A consensus needs to be reached in the near future.

Ethical Issues and End-of-Life Decisions

Treating patients with acute or chronic disorders of consciousness remains a challenging exercise. The debate on the need to continue or stop "futile" treatment in hopeless acute comatose states was started in the 1970s and is now widely accepted

in intensive care. Today, almost half of all deaths in critical care units follow a decision to withhold or withdraw therapy. We know that the chances of significant recovery from chronic unresponsive state are very low 1 year after traumatic and 3 months after nontraumatic brain damage. In these cases, treatment can be considered futile, and its withdrawal can be ethically justified, based on the principles of patient's autonomy, beneficence, and nonmaleficence. For minimally conscious patients, outcome is considered to be better, and at present no time intervals for possible permanency of the condition have been proposed. Recent studies have shown that such patients can recover significant behaviors even years or decades later. No generally accepted standards for care have nevertheless been proposed for patients in minimally conscious state. How should we best care for these patients with chronic disorders of consciousness? Can treatment withholding or withdrawing be justified in some cases? It is generally accepted that competent patients should consent to any treatment they receive and have the right to make choices regarding their bodies and lives. The primary factor determining the level of treatment for an incompetent patient should reflect that patient's personally expressed wishes in his or her situation. But, by definition, coma, unresponsive and minimally conscious patients cannot communicate their wishes.

Regarding locked-in syndrome, the American Academy of Neurology has published a position statement concerning the management of conscious and legally competent patients with profound and permanent paralysis. The conclusion is that such patients have the right to make healthcare decisions about themselves, including whether to accept or refuse life-sustaining therapy – either not start or stop it once started. Doctors caring for patients with locked-in syndrome have "an ethical obligation to minimize subsequent suffering" and should help patients with pain and dyspnea, "even if these medications contribute… to respiratory depression, coma, or death." However, patients should first be fully informed about their condition, and the treatment options and patients' decision must be consistent over a period of time. The latter is clearly necessary to exclude the impulsive transient reactions of despair that are common in patients with severe illness.

What is it like to be minimally conscious? Can patients with severe brain damage experience suffering or satisfaction? What is their quality of life? Is the level and content of consciousness in these patients with such severely damaged brains in any ways comparable to our own? These questions are very hard to answer. Some philosophers might even argue that the subjective aspect of the mind will not ever be sufficiently accounted for by the objective methods of reductionistic science. We prefer a more pragmatic approach and believe that scientific and technological advances will ultimately improve our understanding and management of patients suffering from severe disorders of consciousness.

Pain

Like consciousness, pain is a subjective first person experience. Many patients with severe brain damage cannot communicate their feelings and possible pain perception. The behavioral assessment of motor or autonomic signs (i.e., heart rate,

respiratory frequency, blood pressure, pupillary diameter, and skin conductance) have shown not be reliable indicators of conscious perception of pain (e.g., see studies done in general anesthesia). Pain management in severely brain-damaged patients constitutes a clinical and ethical stake. A European survey showed that the majority of medical professionals thought that patients in a "vegetative state" feel pain. More research is needed to increase our understanding of residual sensation in severely brain-damaged patients and to propose evidence-based medical guidelines for the management of possible pain perception and suffering in these vulnerable patient populations.

Only a few functional neuroimaging studies have studied brain processing linked to noxious stimulation in the unresponsive state. When comparing cerebral activation to high-intensity electrical stimulation of the median nerve at the wrist in 15 unresponsive patients, a preserved and robust activation of the brainstem, thalamus, and primary somatosensory cortex was observed in each and every patient. However, this residual activation was like an island, disconnected from the rest of the "pain matrix" (including the anterior cingulate cortex considered critical in the affective and cognitive processing of pain) and the higher-order cortical network considered necessary for conscious processing. Another study used a similar methodology in seven unresponsive patients and confirmed activation in primary somatosensory cortex but also – and surprisingly – in secondary somatosensory, insular, and anterior cingulate cortices. In the minimally conscious state, results have been more clear-cut and showed that painful stimulation activated the thalamus, somatosensory, insular, frontoparietal, and anterior cingulate cortices. No area was less activated in the minimally conscious patients compared to the studied healthy controls. The observation of a fully activated cerebral "pain matrix" gave objective evidence of a potential pain perception capacity in these patients, stressing the idea that they need analgesic treatment (Fig. 11).

The pros and cons of the use of painkillers in the severely brain-damaged, unable to communicate possible perception of pain, is very complex. Systematic use of narcotic analgesics in disorders of consciousness could lead to sedation and subsequent underestimation of signs of consciousness. On the contrary, some patients might experience hyperalgesia, requiring more aggressive analgesic therapy. Much more research is needed in order to propose scientific-based guidelines. Such research, however, faces major ethical challenges. For some scholars noxious stimuli cannot be applied to patients unable to give written informed consent. In disorders of consciousness, the exploration of behavioral responses to nociceptive stimuli (e.g., applying pressure to the fingernail bed with a pencil, applying pressure to the supraorbital ridge or jaw angle, pinching the trapezium, or rubbing the sternum) is a routine clinical procedure that is used to evaluate the state of consciousness. Reactivity to pain is part of widely used "consciousness scales" such as the Glasgow Coma Scale, and a specific scale was recently developed for patients with severe brain injury, the Nociception Coma Scale-Revised. This new scale is comprised of three subscales: motor, verbal, and facial responses, and a total score between 0 and 9, with a cutoff of 5 for potential pain. This tool allows to identify patients with preserved neural basis for pain experience as evidenced by the total score that

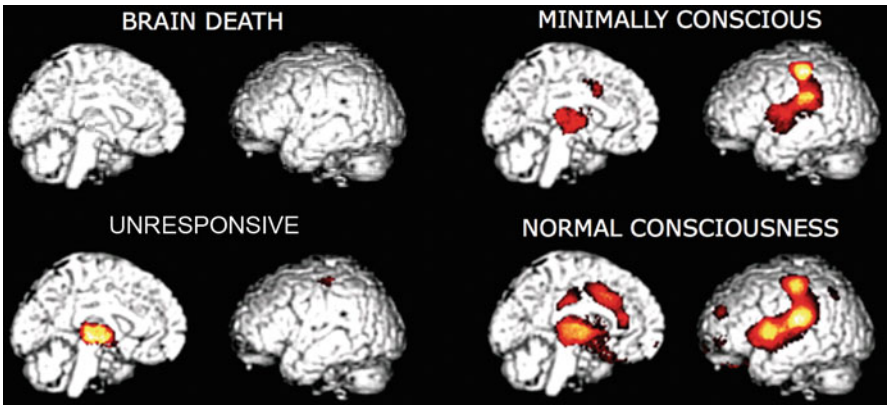

Fig. 11 Brain activation to noxious stimulation in brain death, "vegetative"/unresponsive wakefulness, and minimally conscious states as compared to healthy volunteers. Note (i) the absence of activation in brain death; (ii) the preserved but low-level subcortical and primary cortical activation in the unresponsive state (the primary cortical activation was disconnected from the rest of the brain), and (iii) the near-normal activation in the minimally conscious state

correlates with the metabolism in the anterior cingulate cortex (known to be involved in pain processing).

Caring for severely brain-damaged patients represents such an immense humane, affective, and social problem that it warrants further research to better understand the underlying cerebral function of the severely brain-damaged. Excluding the study of possible residual perception of pain from research protocols would not be ethically justifiable, but they need to be performed within well-defined ethical frameworks based on prudential ethic with respect to dissemination of new scientific methodology and technology, distinguishing investigational from clinical efforts and complementing neuroimaging studies with longitudinal epidemiologic inquiry into the natural history of disorders of consciousness. The ethical implications of these recent technological developments for public policy, emerging therapeutics, and diagnostic and prognostic assessment in these challenging patient populations will also need to be addressed.

Quality of Life

We cannot ask patients with disorders of consciousness about their self-perceived quality of life. However, we can ask locked-in patients who are also fully dependent of others for their daily life activities and survival. Previous studies have evaluated chronic locked-in patients' subjective well-being and the degree to which they are able to return to a "normal" life. Most chronic locked-in patients self-report severe restrictions in community reintegration. Nevertheless, the majority seems to profess "good" subjective well-being (Fig. 12). This is in line with the notion that patients with severe disabilities may report a good quality of life despite being socially

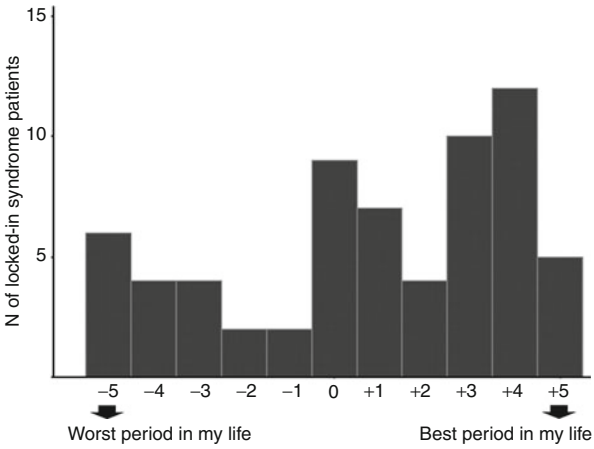

Fig. 12 The majority of chronic locked-in syndrome patients self-report a good quality of life as illustrated using Anamnestic Comparative Self-Assessment scores. Note that control subjects were on average at +2

isolated or having major difficulties in activities of daily living. Interestingly, the longer patients are in a locked-in state, the higher self-reported quality of life seems to be. A minority of chronic locked-in patients declares to have a bad quality of life. Variables associated with unhappiness seem to be dissatisfaction with mobility in the community and anxiety. Studies have also shown that the presence of physical pain is correlated to the frequency of suicidal thoughts. These findings stress the importance (and current frequent inadequacy) of proper anxiety and pain management in chronic locked-in syndrome patients. The demand for euthanasia exists but seems uncommon. The principal clinical conditions for requests for euthanasia or physician-assisted death to be legally valid are "unbearable" suffering and irreversibility of the situation. Whereas the first condition may apply in some locked-in patients, irreversibility cannot be ascertained until, after the acute setting and rehabilitation, their subjective well-being has reached steady state, which may take as long as a year.

Results of studies on quality of life in locked-in syndrome may run contrary to many healthcare professionals. Superficially involved for the short term when the patient is at his or her worst, clinicians may often tend to assume that these persons will die anyway or would choose to die if they only knew what the clinicians knew. As a result, debates about cost, daily management, quality of life, withdrawal or withholding of care, end-of-life decisions, and euthanasia often go on with prejudice and without any input from the conscious but mute and immobile patient. To "judge a book by its cover" is unfair. Clinicians should realize that quality of life often equates with social rather than physical interaction and that the will to live is strong when struck by an acute devastating disease. Evaluating the quality of life of the families of patients is also becoming a focus of research: what needs do they have and are they met? How are they handling this difficult situation? What can we do to help them overcome the obstacles? Involving families' perspectives and experiences into research and clinical work is also now encouraged to get a more holistic approach.

Therapeutic Interventions

Patients with disorders of consciousness are fully dependent on others; they can remain in these states for life, and there is unfortunately not yet a cure for all. Some patients might however benefit from therapeutic interventions, even years after the injury. Up to now, most therapeutic studies are designed as open-label trials and case reports, but several randomized controlled trials have also been performed. Current treatments options are generally divided into pharmacological and brain stimulations interventions.

For pharmacological treatments, only a few drugs have been evaluated so far, and only amantadine has shown some evidence in accelerating recovery in patients with post-traumatic disorders of consciousness. The most intriguing drug is zolpidem (usually taken as a sleeping pill), which induces paradoxical transient improvements of responsiveness in a minority of patients with disorders of consciousness. Only 5% show dramatic positive changes after intake, while 20% may show behavioral improvements but without a change of diagnosis. In three minimally conscious patients who showed drastic improvements such as the recovery of speech or walking, metabolic increases was observed after zolpidem intake in frontal areas (regions involved in motivational processes). Distinctive electroencephalographic patterns (i.e., reduction of low frequency power and coherence, 6–10 Hz) were also observed in three other minimally conscious patients after zolpidem administration. Other drugs such as baclofen have been tested with less success, and others are being investigated such as apomorphine and psilocybin.

The second category of treatments is brain stimulation therapies. Recent work showed the positive effect of prefrontal transcranial direct current stimulation (tDCS) on responsiveness in patients with disorders of consciousness. In the first randomized double-blind sham-control clinical trial (class II level of evidence), tDCS was effective in 50% of patients in minimally conscious state but unsuccessful in unresponsive patients. The effects of tDCS was then tested on other brain regions, such as the motor cortex, the precuneus, and the frontoparietal cortex but with less success. Applying tDCS for 5 consecutive days on the prefrontal cortex of minimally conscious patients show behavioral improvements such as recovery of command-following, and the effects remained for 1 week. Recent application of a home-based tDCS has been developed and can now be used at home and nursing homes.

Possible biomarkers of clinical responsiveness to tDCS have been investigated by means of PET, MRI, and EEG. Responsiveness to tDCS seems to depend on metabolic activity and grey matter integrity of the stimulated brain region but also on the patient's brain connectivity. In a recent case report, an unresponsive patient presented responses to command only after tDCS, and her brain activity was in fact comparable to patients in minimally conscious state. Even when there is no behavioral improvement observed, tDCS can still reduce slow wave activity and modify other neurophysiological markers in patients with disorders of consciousness. Other brain stimulation treatments have shown positive effects in some patients using deep brain stimulation (targeting the thalamus), repetitive transcranial magnetic stimulation, vagal nerve stimulation, and low-intensity focused ultrasound.

Besides interventions to improve consciousness, several recent works focused on motor issues, as most patients with disorders of consciousness present severe spasticity and contractures. These studies demonstrated a link between spasticity and potential signs of pain, the utility of physical therapy, the potential benefit of using tDCS to reduce upper limb hypertonia, and that 30 min of soft splint application can significantly decrease spasticity in chronic patients.

Although new therapeutic approaches have seen the light over this last decade, none has really been able to "switch on" all patients' brains. Optimized stimulation parameters, alternative drugs, and rehabilitation strategies still need to be tested and validated to improve rehabilitation and the quality of life of these patients. Another current challenge is to translate the results from the research into the bench, as we have seen lately that only expert centers are using these therapeutic interventions and it is not yet used in clinical routine.

Neural Signature of Consciousness

In addition to its clinical and ethical importance, studying severely brain-damaged patients offers a still largely underestimated means to the study of human consciousness. The contrastive approach comparing brain activation in circumstances that do or do not give rise to consciousness in either of its two main senses of wakefulness and awareness is now widely applied in functional neuroimaging. In contrast to other unconscious states such as general anesthesia and sleep, where impairment in arousal cannot be disentangled from impairment in awareness, we are here offered a unique lesional approach enabling us to identify the neural correlates of (un) awareness. The discussed neuroimaging and electrophysiology studies are illuminating the relationships between awareness and (i) *global* brain function, (ii) *regional* brain function, (iii) changes in *functional connectivity*, and (iv) primary versus associative cortical activation in response to external stimulation.

For a long time, it is known that arousal is maintained by a diffuse system of upper brainstem and thalamic neurons (called "reticular activating system") and its connections to the cerebral hemispheres. Therefore depression of either brainstem or global hemispherical function may cause reduced wakefulness. Therefore, as we will see, measuring brainstem reflexes are a key to the assessment of coma and the patient's functional integrity of the brainstem's arousal systems. The neural correlate of awareness, however, is only recently better understood. As we will see, it can be regarded as an emergent property of the functional integrity of widespread "higher-order" frontoparietal feedback loops with "lower-level" sensory systems.

Is awareness lost when overall cortical activity falls below a certain threshold? In the unresponsive state, global metabolic activity decreases to about 50% of normal levels – similar to what is observed in anesthesia and deep sleep. However, in patients who recover, global metabolic rates for glucose metabolism do not necessarily show substantial recovery. Hence, the relationship between global levels of brain function and awareness is not absolute. Consciousness is not an emergent property of diffuse global brain function or connectivity. Some areas are more

important than others for its emergence. Nevertheless, with the development of advanced analysis, it is now possible to disentangle minimally conscious state from the unresponsive state looking at the mean cortical metabolism of the best preserved hemisphere. Doing so, it seems that 42% of normal cortical activity represents the minimal energetic requirement for the presence of conscious awareness.

Using voxel-based statistical analyses in the study of severe brain damage, a systematic dysfunction in a wide frontoparietal network was observed when patients might have recovered arousal but lacked conscious awareness. This network encompasses polymodal associative cortices of both the convexity (bilateral dorsolateral prefrontal and posterior parietal areas) and midline (mesiofrontal/anterior cingulate and precuneal/posterior cingulate cortices). These results have been confirmed in other diseases where patients also are seemingly "wakeful" but only show reflex automatic behavior lacking "voluntary" interaction with others – such as absence and complex partial seizures and sleepwalking.

Current analyzing techniques now also permit to assess awareness-related changes in functional integration. Long-range cortico-cortical and cortico-thalamo-cortical "functional disconnections" could be identified in unresponsive patients. Moreover, recovery of awareness after severe brain damage seems paralleled by a functional restoration of this cortico-thalamo-cortical connectivity (i.e., with non-specific intralaminar thalamic nuclei). This understanding culminated in the use of deep brain stimulation therapy to improve awareness in traumatic brain injured minimally conscious patients.

Hemodynamic functional neuroimaging studies (fMRI and PET) using external (noxious or auditory) stimulation showed robust activation in primary and sensory "lower-level" areas which were however isolated and dissociated from the "higher-order" frontoparietal cortical network. The activation in primary cortices in awake but unaware patients confirms Francis Crick's early hypothesis (based on visual perception and monkey histological connectivity) that neural activity in primary cortices is necessary but not sufficient for awareness. This lead to the understanding that cerebral sensory "slave systems" are important for shaping the content of perceptual awareness, but it is the functional integration in the frontoparietal neural workspace that appear critical for the emergence of conscious awareness.

It was also proposed that conscious awareness has two main dimensions: external awareness (i.e., perception coming via our senses) and internal awareness (i.e., stimulus-independent thought, mental imagery, or inner speech). fMRI studies seem to indicate that functional connectivity of the *lateral* frontoparietal workspace network is important for external awareness, while *midline* frontoparietal network connectivity related to internal awareness, known to be the most active "by default" in resting non-stimulated conditions (Fig. 13). Evoked potential studies using dynamic causal modeling in severely brain-damaged patients showed that the top-down "backward" connections from the frontoparietal network seem critical for awareness. Taken together, these studies show that consciousness can be regarded as an emergent property of the collective behavior of frontoparietal top-down functional connectivity.

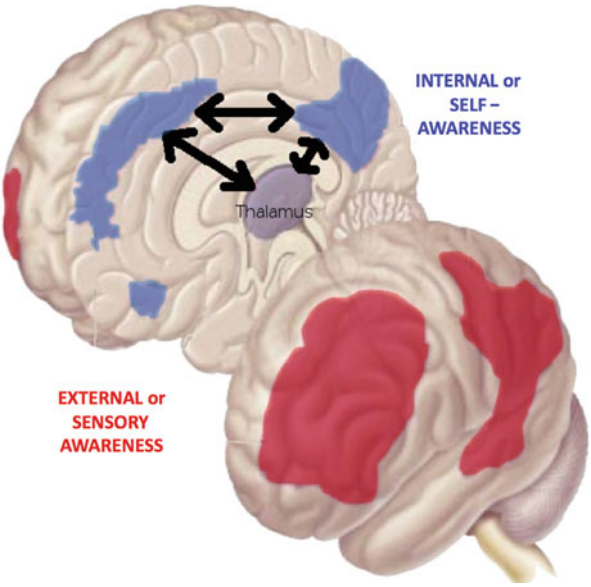

Fig. 13 The frontoparietal "conscious network" can be divided in an external lateral network (in red) critical for external or sensory awareness and an internal midline network (in blue) critical for internal or self-awareness

In parallel, recent works have focused on assessing brain complexity using EEG. EEG studies suggest that entropy measures have diagnostic value in patients with disorders of consciousness and that combining various EEG markers (such as spectral and connectivity measures) with machine learning can reliably identify unresponsive from minimally conscious patients in various contexts (e.g., using resting state or auditory paradigms, using high vs. low-density EEG). Long-duration EEG ultradian rhythmicity can also capture individual differences in patients with disorders of consciousness, and circadian rhythms of unresponsive patients were shown to be more impaired than those of patients in minimally conscious state. EEG brain networks metrics based on graph theoretic methods have also been used recently to predict diagnosis, prognosis, and metabolism of patients with disorders of consciousness.

Combining EEG with transcranial magnetic stimulation (TMS) allows to perturb the brain and see how the brain reacts to the stimulation (using single pulses with an interval inter stimuli of 2 to 3 seconds and looking at the 400 ms after the stimulation). In unresponsive patients, the stimulation usually triggers a stereotyped slow wave and local response, as in deep sleep and general anesthesia. In contrast, in minimally conscious patients, the stimulation triggers rapidly changing and long-lasting widespread responses, as it is observed in normal wakefulness and in patients with locked-in syndrome. The perturbational complexity index was recently developed to quantify the observed responses with TMS-EEG in pathological condition (post-coma) but also in pharmacological (anesthesia) and physiological (sleep) conditions. This index is thus a measure of complexity that gauges TMS-EEG spatiotemporal diversity at the scalp or the source level, which provides an

operational threshold that differentiates conscious from unconscious patients with a high sensitivity and specificity. Indeed, unconscious patients have a low value of the perturbation complexity index (i.e., lower than 0.31), while (minimally) conscious patients have a high value (i.e., higher than 0.31). Some unresponsive patients have however also a high value, which suggest that they have the capacity to be conscious, and preliminary evidence shows that they may recover sign of consciousness compared to unresponsive patients with lower values.

Recently, scientists have provided reference and common ground about EEG techniques for the prognostic and diagnostic assessment of patients with disorders of consciousness, for both researchers active in the field of neurophysiology and clinicians engaged in intensive care unit.

Other recent work used resting state fMRI connectivity and user-independent automated classifiers to differentiate between unresponsive and minimally conscious patients. More specifically, the default mode, frontoparietal, salience, auditory, sensorimotor, and visual networks have all a high discriminative capacity (>80%) for classifying these patients. Among these different resting state networks, it is the auditory network that was ranked the most highly. The regions of the auditory network which were more functionally connected in patients in minimally conscious state compared to unresponsive patients included bilateral auditory and visual cortices. These findings point to the significance of preserved abilities for multisensory integration and top-down processing in minimal conscious patient, which is seemingly supported by auditory-visual crossmodal connectivity. Additionally, patients with impaired consciousness appear to suffer from abnormally increased inter-network correlations, while only patients who recovered from the minimally conscious state show partial preservation of fMRI "anticorrelations" between resting connectivity networks (especially between the default mode network and the frontoparietal network). Lastly, the study of brain dynamics (as opposed to "static analysis") is becoming trendy. Recent work demonstrated that minimally conscious patients have a dynamic pattern of coordinated and anticoordinated fMRI signals, whereas unresponsive patients showed primarily a pattern of low interareal phase coherence mainly mediated by structural connectivity, with smaller chances to transition between different patterns.

Of clinical importance, all this knowledge now permits to improve the diagnosis of patients with disorders of consciousness, which, as we have seen, remains very challenging at the bedside. As discussed, current technology and knowledge now also permits to show command-specific changes in EEG or fMRI signals providing motor-independent evidence of conscious thoughts and in some cases even of communication.

Outlook

Some patients who awaken from their coma may fail to show any behavioral sign of awareness (i.e., they are considered to unresponsive), or they may remain unable to communicate (i.e., are in a minimally conscious state). The clinical management

of these disorders of consciousness remains very challenging, but technological advances in neuroimaging are now offering new ways to improve our diagnosis. New European and American guidelines have also been recently published regarding diagnosis, prognosis, and care recommendations for patients with disorders of consciousness. It is an exciting time as the behaviorally defined gray zones between the different disorders of consciousness in the clinical spectrum following coma are being challenged by increasingly powerful imaging technology. For the first time, neurologists may encounter rare but existing cases of cognitive-motor dissociation or MCS*, where only paraclinical tests permit to demonstrate the presence of higher cognitive function, inaccessible to our motor-dependent clinical evaluations.

In a not so far future, real-time fMRI-based communication or evoked potential brain computer interfaces will be used to address important clinical and ethical questions such as feeling of pain and discomfort. These novel technological means will undoubtedly further improve the existing nosology and clinical care of these challenging patients with disorders of consciousness.

In a fraction of patients who are currently considered to be clinically unresponsive, functional MRI, event-related potential or electromyography techniques can now reveal signs of consciousness that are unattainable by bedside clinical assessment. These novel tools urgently need to be introduced into clinical practice so that each patient can benefit from the scientific and technological advances. These discoveries will most likely change the existing behaviorally defined boundaries between the various consciousness disorders. These high-tech devices will permit some of these clinically "noncommunicative" patients to share their thoughts and wishes via nonmotor pathways. However, before entering into clinical routine, we have to think about the ethical concerns associated with these advances. We side with a proposed ethical framework that emphasizes the need to achieve a balance between the protection of patients with disorders of consciousness and the ability to perform research that can lead to medical progress. Most of the advances in coma science are still based on small cohort or even single-case studies. Only large-scale multicenter clinical trials will enable these research tools as well as future therapeutic options to find their way into evidence-based care for individuals with a disorder of consciousness following severe brain damage.

Videos

- Communication via fMRI
- Showing signs of consciousness using High-density EEG
- Studying memories and near death experiences https://www.facebook.com/ComaScienceGroup/videos/1234759753202494/.
- From brain to consciousness: Steven Laureys at TEDxBrussels: https://www.youtube.com/watch?v=6Qqc_wJS6-Q&t
- Stimulating the damaged brain: Steven Laureys at TEDxUNamur: https://www.youtube.com/watch?v=ISXf8NVlP7Q
- Coma and Consciousness: Steven Laureys at TEDxParis.
- https://www.youtube.com/watch?v=jqEq0Nt7MvM

- Consciousness and complexity (assessed with the perturbational complexity index): https://www.youtube.com/watch?v=1-bJKLA_KaA
- Generet price of Steven Laureys: https://www.youtube.com/watch?v=ss2fFNxehN8
- Dance your PhD 2018: the (un)conscious brain – Measuring consciousness after severe brain injury using brain stimulation: https://www.youtube.com/watch?v=eYMmVNei2Hc&t

References

Sanz LRD, Aubinet C, Cassol H, Bodart O, Wannez S, Bonin EAC, Barra A, Lejeune N, Martial C, Chatelle C, Ledoux D, Laureys S, Thibaut A, Gosseries O (2021) SECONDs administration guidelines: a fast tool to assess consciousness in brain-injured patients. J Vis Exp (168)

Thibaut A, Schiff N, Giacino J, Laureys S, Gosseries O (2019) Therapeutic interventions in patients with prolonged disorders of consciousness. Lancet Neurol 18(6):600–614