The changing spectrum of coma

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Modern intensive care can sustain most of the body's vital functions after severe brain injury, except for those of the brain, and modern technology has dramatically increased acute survival in this setting. When some patients awake from their coma, however, they fail to show any signs of awareness or voluntary behavior (i.e. they are in a vegetative state), or they remain unable to consistently and reliably communicate their thoughts and wishes (i.e. they are in a minimally conscious state). The clinical management of these disorders of consciousness remains very difficult, but technological advances in neuroimaging and in EEG-based brain–computer interfaces are now offering new ways to improve the diagnostic, prognostic and therapeutic management of these challenging conditions. Here, we will discuss some recent studies that we believe are heralding a new era of coma research and management.

Historically, the seat of consciousness was widely believed to be in the heart, and the absence of heartbeat was regarded as the clinical sign of death. Neuroscientific evidence has superseded such thinking and has shown that consciousness, an emergent property of neural activity, resides in the brain.[1] Since the invention of the positive-pressure mechanical respirator, it has become possible to sustain cardiorespiratory function in individuals who are in a coma, so that research can focus on brain function as a separate entity. Patients who would previously have died from apnea are now able to survive in profound comatose states that had never been encountered before. This technological progress forced modern medicine to redefine the diagnosis of death and move from its ancient cardiorespiratory-centered definition to a neurocentric one, where death is defined as the irreversible loss of all brainstem reflexes (including the breathing reflex). Since the introduction of this clinical definition, not a single patient who fulfils the criteria of brain death has ever regained consciousness.

Patients who recover from coma can transit through different clinical stages (Figure 1). The vegetative state is characterized by the recovery of arousal systems (clinically defined by the presence of eye opening), whereas all motor behavior remains reflexive (i.e. the patient shows no signs of awareness).[2] Some patients in the vegetative state might remain in this condition permanently. Others, however, might show progressive recovery of nonreflex behavior. The recognition of a condition in which patients show reproducible but inconsistent signs of command-following or voluntary behavior, but fail to show functional communication, prompted the medical community to add a new clinical entity to the spectrum of disorders of consciousness; in 2002 the Aspen Neurobehavioral Conference Workgroup referred to this condition as the 'minimally conscious state'.[3]

The origin of coma research as a science probably dates to 1966 when Fred Plum and Jerome Posner published the first edition of their classic text *The Diagnosis of Stupor and Coma* (for the 2007 edition see Posner *et al.*[4]). For the first time, researchers correlated clinical findings that were derived from the examination of patients in comatose states with pathological findings, and they proposed a pathophysiological explanation of altered consciousness. In 1974, Bryan Jennett and colleagues published the Glasgow Coma Scale[5] and, in the next year, the Glasgow Outcome Scale[6]. These standardized scoring systems enabled the performance of multicenter clinical trials and epidemiological studies that resulted in the development of rational algorithms for the treatment (or withdrawal thereof) of comatose patients.

Pioneers such as Jennett and Plum revolutionized the field of acute brain injury. However, the excitement of the 1970s was followed by a return to therapeutic nihilism (i.e. the assumption that patients with chronic disorders of consciousness are uniformly hopeless cases) and a marked decrease of scientific interest in disorders of consciousness. Coma research nearly became comatose. Only recently, partly incited by advances in the field of functional

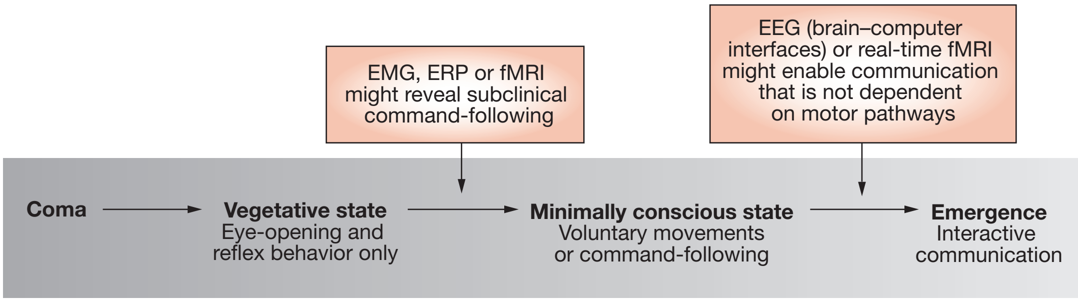

Figure 1 Patients in a coma might progress to a vegetative state (clinically defined as wakefulness solely accompanied by reflex behavior). Next, patients might transition to a minimally conscious state (i.e. the patient shows signs of command-following or other nonreflexive movements). The restoration of interactive communication indicates the emergence from the minimally conscious state. Novel technological means are changing these behaviorally defined boundaries. In the future, EMG, ERP and fMRI techniques might reveal signs of consciousness that are unattainable by bedside clinical assessment in a yet to be discovered fraction of patients who are currently considered to be vegetative. In a next step, these high-tech devices might permit some of these patients to communicate their thoughts and wishes via nonmotor pathways. Abbreviations: EMG, electromyography; ERP, event-related potential; fMRI, functional MRI.

neuroimaging, did the study of coma and related states undergo a revival.

The clinical studies conducted since the 1970s have illustrated how challenging it is to disentangle reflex behavior from voluntary behavior—a problem that can potentially lead to diagnostic error. We are confined to inferring the presence of awareness from a patient's motor responsiveness. Functional neuroimaging now offers the possibility of directly measuring the brain's activity, not only at rest or during passive stimulation, but also in response to commands.[7] The potential of this technique, the best so far to unequivocally prove the presence of consciousness, was illustrated by the extraordinary case of a patient who was able to imagine playing tennis, as demonstrated by functional MRI, while showing no clinical sign of awareness whatsoever.[8] This case illustrates that novel neuroimaging methods can now be used to detect signs of consciousness in noncommunicative patients with brain damage. This possibility can lead to radical changes in a patient's diagnosis and, hence, in his or her management (it should be noted that some months after the study, the reported patient also showed behavioral signs of recovery).

In many patients with disorders of consciousness, it is difficult to reliably predict the chances of functional recovery. However, MRI techniques such as spectroscopy and diffusion tensor imaging have improved the quantification of neuronal damage. Furthermore, diffusion tensor imaging recently revealed axonal regrowth in a patient who had been in a minimally conscious state but recovered verbal communication nearly two decades after a traumatic brain injury.[9] This demonstration of axonal regrowth after such a long time interval disproved the old dogma that neural plasticity is limited to the acute or subacute phase of cerebral injury.

Finally, the widespread therapeutic nihilism with regards to chronic disorders of consciousness has been challenged by new evidence derived from the use of deep brain stimulation. A patient who was in a minimally conscious state underwent bilateral thalamic stimulation more than 6 years after acute trauma; the intervention improved the patient's cognitive function and resulted in a return to functional object use and intelligible verbalization.[10] The usefulness of deep brain stimulation in this setting awaits confirmation from studies that include larger cohorts of patients, but the evidence to date offers hope that the technique can represent a real therapeutic option in well-chosen patients (selected on the basis of functional neuroimaging results).

In the recovery from coma, the acquisition of interactive verbal or nonverbal communication represents an important milestone—the ability to communicate their wishes concerning treatment options enables these vulnerable patients to exert their right to autonomy. Rapid advances in the development of EEG-based brain–computer interfaces mean that clinically noncommunicative coma survivors can finally have a voice of their own.[11] We predict that real-time functional MRI and EEG-mediated technology will offer these patients non-muscle-dependent channels of communication, enabling them to express their thoughts, control their environment and improve their quality of life.

Clearly, it is a thrilling time for the field of acute brain injury. The gray zones between the different disorders of consciousness in the clinical spectrum following coma are beginning to be better defined by the addition of powerful imaging methodology to bedside clinical assessment. We foresee that in a yet to be discovered fraction of patients who are currently considered to be vegetative, electromyography, event-related potential and functional MRI techniques will reveal signs of consciousness that are unattainable by bedside clinical assessment. These novel technological means will change the existing behaviorally defined boundaries between the various consciousness disorders. In a next step, these high-tech devices will permit some of these clinically 'noncommunicative' patients to convey their thoughts and wishes via nonmotor pathways. However, it should be stressed that these exciting developments are not yet a reality. The first hurdle that needs to be overcome before the methodologies discussed above can enter clinical practice relates to ethical concerns. 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.[12] Most of the advances in coma science discussed above are based on single-case studies. Only large-scale, multicenter clinical trials will enable these research tools to find their way into evidence-based care and really influence the lives of individuals with severe acquired brain damage who have a disorder of consciousness.

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Competing interests
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