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Chronic disorders of consciousness (Review)

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Abstract. Over the last 20 years, studies have provided greater insight into disorders of consciousness (DOC), also known as altered state of consciousness. Increased brain residual functions have been identified in patients with DOC due to the successful application of novel next-generation imaging technologies. Many unconscious patients have now been confirmed to retain considerable cognitive functions. It is hoped that greater insight regarding the psychological state of patients may be achieved through the use of functional magnetic resonance imaging and brain-computer interfaces. However, issues surrounding the research and treatment of DOC remain problematic. These include differing opinions on the definition of consciousness, difficulties in diagnosis, assessment, prognosis and/or treatment, and newly emerging ethical, legal and social issues. To overcome these, appropriate care must be offered to patients with DOC by clinicians and families, as DOC patients may now be considered to live in more than just a vegetative state. The present article reviews the controversy surrounding the definition of consciousness and the reliability of novel technologies, prognostic prediction, communication with DOC patients and treatment methods. The ethical and social issues surrounding the treatment of DOC and future perspectives are also considered.

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Key words: disorders of consciousness, vegetative state, unresponsive wakefulness syndrome, minimally conscious state

Contents

1. Introduction

Developments in modern emergency treatments and life-support systems have substantially improved the treatment of severe trauma or cardiac accidents for millions of patients. Traumatic brain injury-related mortality has reduced from 17% in 2000 to 11% in 2010, as reported by Siman-Tov, *et al* (1). However, 10-15% of patients who sustain severe acquired brain injury enter a condition termed a disorder of consciousness (DOC), which broadly includes the syndromes of coma, vegetative state [VS; also known as unresponsive wakefulness syndrome (UWS)] and minimally conscious state (MCS) (2,3). Over the past century, there have been few methods that reliably assess the consciousness of DOC patients, as methods of traditional behavioral assessment may be easily limited. In DOC patients, responses to command may be only minimal or inconsistently present and can be very difficult to identify clinically. This may be a primary factor contributing to a ~40% misdiagnosis rate for VS (4).

However, recent advances in neuroimaging, such as functional magnetic resonance imaging (fMRI) and brain computer interface (BCI) have improved the identification of residual cognition in DOC patients (5). These recently developed techniques have provided novel insights into the brain function of DOC patients and may partly complement the clinical behavioral assessment. They may also be employed to examine the effects of certain therapeutic interventions, including pharmacological agents, brain stimulations and music training (5,6). In the current article, advances in the clinical assessment of DOC patients are reviewed, in addition to current concerns and future perspectives in the treatment of DOC.

2. Controversy over the concept of consciousness

Due to improvements in emergency therapy, particularly in life-support systems, the mortality rates of patients with severe head trauma or cardiac arrest have been markedly decreased (1). However, 10-15% patients who survive the acute coma stage enter into a chronic DOC (2,3). Therefore, the treatment and rehabilitation of patients with DOC is a major challenge in clinical neuroscience. As a pre-requisite for effective treatment, an objective assessment of the conscious state of DOC patients is necessary, which has been a focus of research from both clinical and neuroscience perspectives (7).

A plausible definition of consciousness limits the in-depth investigation of DOC that may otherwise provide insight into the different states of consciousness. Several definitions of consciousness have so far been proposed (8). A commonly accepted viewpoint is that consciousness is the brain's ability to form cognition of the world, including sensations and perceptions of oneself and the environment. The majority of researchers believe that consciousness can be separated into a minimum of two components; wakefulness and awareness. The former refers to the level of consciousness and the latter the content of consciousness. The majority of patients with traumatic brain injuries transit through the following states of consciousness during recovery: Coma, VS (UWS), MCS and emergence from MCS. This recovery path is consistent with the two aspects of consciousness, as first the level of consciousness is recovered, which is then succeeded by re-building of its contents (9,10). This is indicated by the recovery of DOC patients, of which there are two contradicting nomenclatures (Fig. 1). One is functional locked-in syndrome (fLiS), the other is functional MCS (fMCS). Locked-in syndrome (LiS) is caused by an insult to the ventral pons, most commonly an infarct, haemorrhage or trauma. The typical signs of LiS are quadriplegia and anarthria with preservation of consciousness and vertical eye movement, facilitating non-verbal communication. Bauer *et al* (11) reviewed the history of LiS and divided it into three types: classical LiS (total immobility with the exception of vertical eye movements and blinking), incomplete LiS (If any other movements are present) and total LiS (total immobility, including all eye movements, combined with signs of undisturbed cortical function in the EEG). The neuroanatomical basis of LiS was also analyzed and it was indicated that a de-efferented state with preserved consciousness appears to be possible with lesions in both cerebral peduncles (11). This state may preserve all or partial consciousness, detected using modern neuroimaging technologies, which demonstrate functional communication (active paradigm) and between-network anti-correlation (passive paradigm) (12). The present study therefore hypothesized that fLiS should be kept as a separate nomenclature for this state and as one member of the LiS sequence. To be consistent with the classification of other MCS (MCS- and MCS+), Gosseries *et al* (13) proposed MCS* as an indicator of VS with covert awareness. However, para-clinical tests indicate no functional communication and no between-network anti-correlation in patients with fMCS (12).

Consciousness, however, may not simply consist of two dimensions (14). Laureys and Schiff (15) proposed a revised recovery path of DOC, which due to its complexity is difficult to accurately replicate. Monti (16) thus proposed that alternative recovery behavior belonged to a third dimension of consciousness; however, not all types of DOC can be accurately described by the improved model. Therefore, other dimensions are considered to support consciousness, including those depicted in Fig. 2 (9,10). With the exception of the familiar concepts such as level of consciousness (wakefulness) and content of consciousness (awareness), behavior, degree and range were also proposed as dimensions of consciousness (9,14). It is therefore possible that more dimensions may exist (Fig. 2).

3. Reliability of novel diagnostic technologies

Given the uncertainty surrounding the definition of consciousness, difficulties remain in the diagnosis and assessment of DOC. Behavioral assessment is considered to be a golden standard method for evaluating the awareness of patients with DOC (7). Various other methods, including skin conductance response (SCR), diameter of the pupils, breathing control and mini movement micro-switch have also been proposed to advance the diagnosis and assessment of DOC (17-20). According to the Coma Recovery Scale-Revised (CRS-R), any early signs, including visual fixation, visual pursuit and pain location, may aid to determine whether a patient has transited from VS to MCS (4). However, the rate of clinical misdiagnosis based on the CRS-R remains high, due to subjectivity of the evaluator and the physical status of the patient (21).

With the development of positron emission tomography (PET), fMRI and electroencephalographic (EEG) recording of event related potentials (ERP), detection and analysis of brain activity signals are now possible in clinical practice (22). In turn, these techniques may enable the detection of residual cognitive brain functions in DOC patients. Previous results have demonstrated that 17-19% of patients may be distinguished from VS/UWS by the detection of brain activity changes with fMRI or EEG (23). In turn, this patient ratio was increased up to 33% with the use of Sitt's automatic classification of the state of consciousness (24). Therefore, previous evaluations based on behavior may have underestimated the brain function of DOC patients.

Brain activity may become a target for evaluation of consciousness, as neuroimaging techniques are able to detect cognitive function by decoding conscious responses based on brain activity (25). Advances in computer science have also made a form of communication with DOC patients possible, by modulating the brain activity or through the control of electrical brain activity (26). With the development of these novel imaging methods, the current guideline or consensus on behavior-based diagnosis and evaluation should be revised in order to progress and allow these newly developed imaging techniques to be considered in discussing the diagnoses, treatment and prognosis of DOC. However, cognitive function detected by current technologies is still unable to reliably prove the consciousness of a DOC patient. Brain activity alone cannot prove patient consciousness,

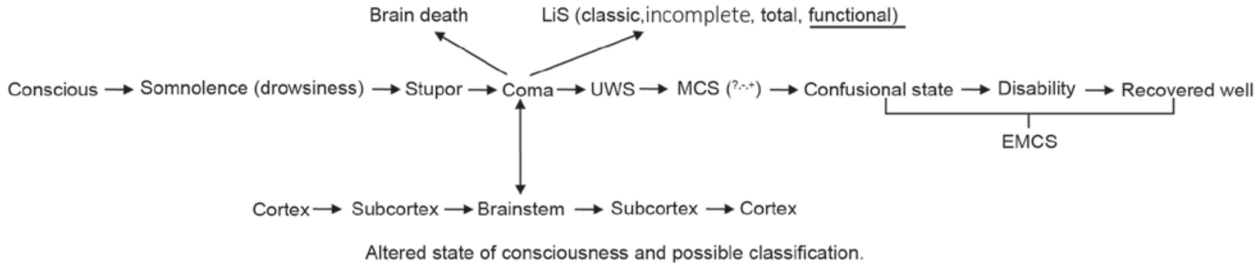

Figure 1. Possible classification for altered state of consciousness and pathology. LiS is a specialized nomenclature in which the lesion is localized in different areas of the brain stem (11) and therefore it is suggested that functional LiS is placed into the LiS sequence. While it is suggested that patients with limited cognitive brain function are diagnosed using para-clinical testing are placed prior to MCS^- and diagnosed differently, here $MCS^?$ is a substitute for $MCS^=$ or MSC^* (12). LiS, locked-in syndrome; MCS, minimally conscious state; MCS^+, minimally conscious state plus; MCS^-, minimally conscious state minus; $MCS^?$, vegetative state with covert awareness and substitute for the undetermined name MCS* or $MCS^=$; EMCS, emergence from MCS; UWS, unresponsive wakefulness syndrome.

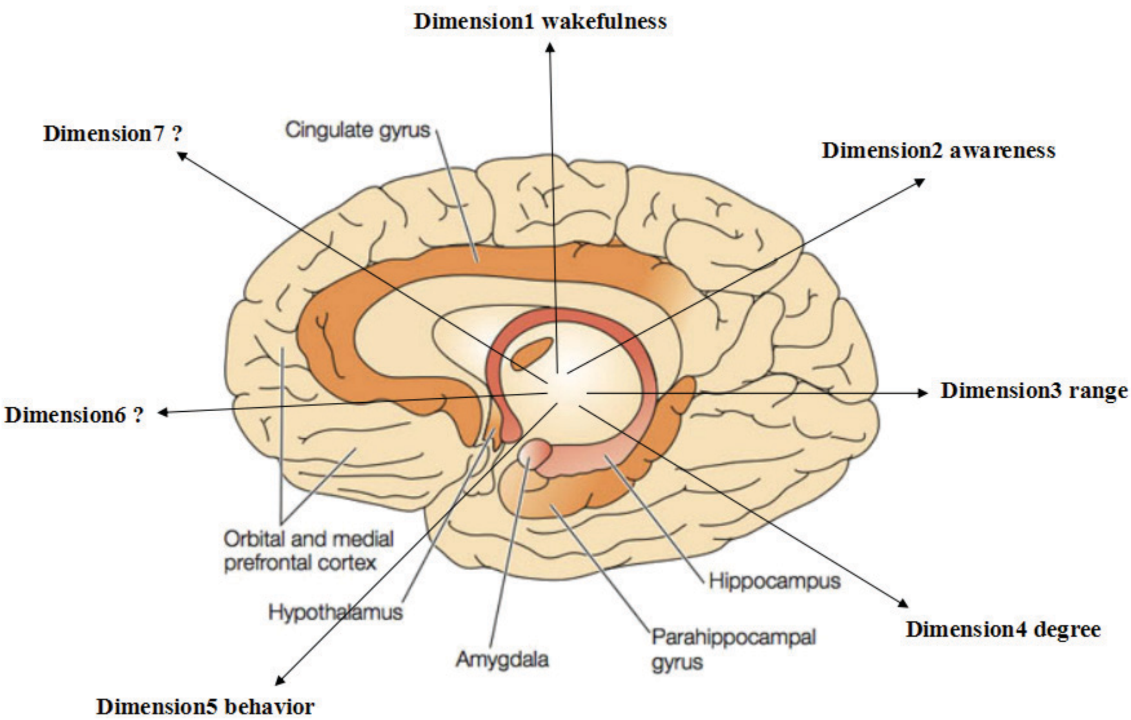

Figure 2. Potential multiple dimensions of consciousness.

though it has been hypothesized that consciousness is associated with brain activity (27). Importantly, a fundamental distinction between consciousness and unconsciousness is yet to be determined. This should be defined based on a more feasible, sensitive and accurate diagnostic criteria, built on a combination of the available behavioral, brain imaging and electrophysiological measures.

4. Prognosis of DOC patients

Prognosis is also a concern for DOC patients. Classical prognostic indicators include age, etiology, coma period, CRS-R or Disability Rating Scale (DRS), S100 protein and neuron-specific enolase (NSE) expression and N20 neuron potential. CRS-R or DRS scores are associated with patient prognosis and have a marked predictive power with respect to the time until commands are followed (28).

According to the biomarkers, NSE and S-100B are released following injury to neurons and glial cells respectively and are likely to be associated with the extent of anoxic-ischemic neurological injury following cardiac arrest and therefore, with the severity of neurological outcome (29,30). Median nerve somatosensory evoked potentials (SEPs; primarily N20) also provide useful prognostic information regarding the outcome following coma and are becoming increasingly used (31,32).

The development of PET, fMRI, EEG and BCI has made it possible to predict the prognosis of DOC patients. For instance, Vogel *et al* (33) tested active signals within regions of interest (ROIs) of 22 DOC patients using a mental imagery fMRI paradigm. It was suggested that VS patients with ROIs that were activated significantly had the potential to recover from DOC to MCS at minimum, while those with inactivated ROIs were likely to remain in VS. In addition, Luyt *et al* (34) analyzed Diffusion Tensor Imaging results of 57 post-cardiopulmonary resuscitation patients two weeks after entering a coma, revealing that the specificity and sensibility of the Fractional Anisotropy index as a one-year prognostic indicator were 100 and 94%, respectively.

Di *et al* (35) also systematically reviewed previous studies on the use of PET and fMRI in DOC patients, and based on results, classified the neuroimaging activation into three patterns: Absence of cortical activation, typical low-level primary cortical activation and higher level associative cortical activation. The latter high level activation mode was demonstrated to predict recovery from VS with 93% specificity and 69% sensitivity.

EEG is also a simple and effective method of detecting brain function in DOC patients, and Lehembre *et al* (36) suggested that quantitative EEG may be a useful way of distinguishing MCS from VS/UWS. In addition, Qin *et al* (37) and Cavinato *et al* (38) evaluated the prognostic values of cognitive event-related potential (ERP). It was observed that MMN and P300, evoked by the subject's own name, exhibited potential prognostic values in predicting recovery of consciousness and therefore, they may serve as good prognostic markers. However, through the use of active task paradigms, it may be possible to determine whether a patient has an appropriate level of residual brain function to process stimulation, and thus if they are likely to regain consciousness (39). However, current technology remains unable to accurately determine the prognosis of DOC patients. Future multi-center studies are warranted to determine the efficacy of novel neuroimaging technologies as prognostic indicators in DOC.

5. Communication with DOC patients

Communication with DOC patients is now possible due to the aforementioned imaging technologies, particularly with fMRI. Owen *et al* (40) were among the first to establish successful communication with DOC patients using real-time fMRI combined with mental imaging stimuli, demonstrating the possibility of binary communication with DOC patients through use of their residual brain functions. Although these results are controversial due to the voluntary activation of task-specific brain areas in response to passive exposure to stimuli associated with a specific action can be with or without conscious awareness, they are considered to be a key paradigm in DOC research (41).

However, there are limitations to the application of fMRI in the management of DOC, including high cost, immobility, inconvenience of operation and a complicated operational procedure (42). Other non-invasive methods are therefore employed for communication with DOC patients, including EEG and functional near-infrared spectroscopy (fNISS). Naci *et al* (43) compared the efficacy of fMRI, FNISS and EEG with BCI and observed that EEG may be a suitable method of communication. Although EEG signals are affected by involuntary muscle or eye movements and has limited spatial resolution, particularly within deep brain structures, EEG has a number of advantages over other methods such as fMRI and PET, including low cost, noninvasiveness, a relatively simple operational procedure, high temporal resolution and further BCI applications (42). Thus, EEG may be an ideal communicative apparatus.

BCI based around EEG is used to evaluate the different components identified by EEG, including P3 potential, sensorimotor rhythm, also known as mu-rhythm, and slow cortical potentials (44). Münßinger *et al* (45) assessed two different versions of the P300-Brain Painting application: A colored matrix in 3 ALS-patients and 10 healthy participants, and a black and white matrix assessed by 10 healthy participants. The ALS-patients were able to use the application with the same accuracy as healthy subjects and greatly enjoyed P300-Brain Painting. Coyle *et al* (46) also used image-based BCI to examine the effect of real-time feedback in an MCS patient. It was revealed that, with no feedback, two motor imagery (MI; hand grasp vs. toe movement) could be classified with ~82% accuracy with only three EEG channels. When providing real-time feedback with two games where the participant was instructed to move a ball and a spaceship respectively, to reach a target by performing the same MI tasks, 77.5% ball and 80% spaceship control were achieved. This means real-time feedback may be used in the detection of awareness and as a means of communication.

The aforementioned studies indicate the preliminary applications of BCI in DOC patients. As nearly 20% of the accuracy obtained by potential users does not reach criterion level, BCI control is not currently accurate enough for clinical use (47). Despite the requirement for further adaptation of BCI to patients with disorders of consciousness, this assisted communication technology does, however, provide insight into the cognitive state of DOC patients. With future improvements in the design of BCI paradigms, it may be possible to elucidate the cognitive function of DOC patients, particularly regarding their decision-making processes. Verbal communication with DOC patients may also become possible with improved BCI techniques (48,49).

6. Future therapies for DOC patients

Although there have been advances in research regarding the treatment of DOC, there remain few effective therapies in clinical use. In clinical trials, several drugs have been documented to improve motor ability and cognitive functions, including Bromocrirtine, Levodopa, Baclofen, Chalybeate, Zolpidem, Apomorphine, Ritalin, Meclofenoxate and Amantadine (50). However, no drugs have been further approved thus far. Therefore basic life support, including sufficient hydration and nutrition, remain the recommended therapeutic strategies for patients with DOC in China (51).

An alternative therapeutic method is neural stimulation, including median nerve electrical stimulation, cervical spinal cord stimulation to the dorsal column and deep brain stimulation to the central thalamic nuclei (52). These methods have been demonstrated to alleviate the restrictions in functional communication, motor performance, feeding and object naming experienced by DOC patients, particularly in MCS patients with traumatic brain injuries (53). In addition, the administration of transcranial direct current stimulation in DOC has exhibited promising rehabilitative effects, particularly within the left dorsolateral prefrontal cortex in MCS patients following severe brain damage (54).

The significance of the aforementioned studies remains to be elucidated by large sample clinical trials, as their applications are currently questioned (55). Effective therapies for DOC are expected to emerge with improved understanding of brain function, which in turn warrants further study. In the future, a combination therapy involving medicine, physical stimuli and genetic/cell therapy may be a viable therapeutic option in the treatment of DOC.

7. Ethical, legal and social issues

Ethical, legal and social issues have arisen due to the lack of effective therapies for VS/UWS. A principal controversy is the decision to end life support for VS/UWS patients, particularly those deemed to be permanent VS patients (remaining in an unconsciousness state for one year following traumatic injury or three months following non-traumatic injury) (56). Whether any one individual should be responsible for the survival or mortality of DOC patients is also questioned by clinicians and lawyers. Patient caregivers additionally present ethical and social issues, due to concerns over their physical and psychological state, attitude toward patients and economical or social pressures. Views of the patient are also difficult to obtain, and even with novel technologies, the only communications currently possible are binary 'yes or no' choices (57-60).

Furthermore, as the cognitive functions of DOC patients are severely compromised, and their expressions may be inaccurate. Indeed, it has been suggested that concerns regarding the ethical treatment and social needs of patients should be expressed by relatives and guardians, despite the development of novel technologies (61).

The quality of life of DOC patients is also questioned, although a previous study in patients with locked-in syndrome (LIS) contradicts traditional views that DOC patients have a low quality of life (62). Specifically, the study by Bruno *et al* (62) documented that 72% of LIS patients stated their lives were meaningful despite their living in social isolation or being severely disabled, while only 28% of patients declared that they were unhappy. It has also been reported that VS/UWS patients may experience pain following electrical stimulation of the median nerve (63), indicating that VS/UWS patients may benefit from additional therapy, such as analgesia. Thus, patient quality of life as well as survival should be considered in the long-term treatment of DOC. Optimizing the aforementioned technologies in the diagnosis and treatment of DOC may be useful in addressing these ethical and social issues.

8. Current limitations and future perspectives

Although there have been advances in experimental research on DOC, their detailed underlying mechanisms remain to be elucidated, and existing classification systems are unable to describe all clinical sub-types. In addition, the efficacy of novel neuroimaging technologies regarding the diagnosis, prognostic assessment and treatment of DOC require verification from large-sample clinical trials. The ethical, legal and social issues associated with DOC should also be addressed alongside the development of clinical methods.

Clinical-based studies may aid to determine the efficacy of neuroimaging methods. Specifically, studies that combine assessments of behavior and brain activity using BCI are warranted, which first requires improvements in current BCI technology. Increased understanding of residual cognitive functions may also aid the diagnosis, treatment and prognostic evaluation of DOC patients. The ethical and social issues concerning the quality of life, survival and treatment of DOC patients should also be considered rather than solely their physical condition.

In China, ethical and clinical guidelines, similar to those formulated by Coleman and Dolce (64), should be formulated for Chinese DOC patients by multi-disciplinary DOC research groups. Regular consultations across departments, including neurology, neurosurgery and neurological rehabilitation and intensive care units, may aid to better conserve brain function during the early stages of brain injury, potentially reducing the risk of DOC. In addition, Chinese epidemiological surveys are warranted to obtain data that may aid in decision-making by the government: For example, the incidence and prevalence of DOCs, the average cost of a chronic DOC patient in one year and the caregivers' burden (65), which are all worthy of consideration when discussing public health expenditure. In addition, internet-based DOC associations, comprised of doctors, patients, relatives and social workers, may facilitate information exchange, education and communication between clinicians, relatives and caregivers.

9. Conclusion

Our group is the first clinical DOC research group in China and has established a coma recovery unit in the Institute of Neuroscience, which has thus treated 60-80 DOC patients annually. Multi-disciplinary studies including functional neuroimaging and electrophysiological recording, namely PET, fMRI and BCI, have also been performed in our laboratory (66,67). In addition, our group has established cooperation among research institutes and non-governmental organizations to promote the welfare of DOC patients, with an ultimate goal of establishing the first DOC society in China. For DOC patients, therapy alone is unable to resolve all the issues presented by altered conscious states, even after the emergence of novel technologies. Thus, provision of humanistic care for DOC patients and their relatives is currently the primary goal in the treatment of DOC.

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