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EDITORIAL

Recent Progress in Basic and Clinical Research on Disorders of Consciousness

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Severe brain injury can lead to disorders of consciousness (DOCs). Since DOC patients cannot communicate functionally or behave purposefully, most remain bedridden and require laborious care. The medical community is often confronted with the expectations of the families of chronic DOC patients, and the social, economic, and ethical consequences are tremendous. Research on DOCs is attracting increasing attention from scientists and physicians in various fields. With the development of modern neuroimaging and neuromodulation techniques, much progress has been made in the diagnosis, prognosis, treatment, and rehabilitation of DOCs in the last decade.

This issue aims to summarize the progress in studies of DOCs in China. Zhao reviews the present status of DOC studies in China, specifically concerning diagnosis, prognosis, therapy, and rehabilitation. He also introduces the development of DOC-related scientific organizations and activities in China [1]. This provides a clear picture of the role China is playing in DOC research.

The Brainnetome, based on neuroimaging, has opened new opportunities to study the neural correlates of consciousness, and provides additional information concerning the diagnosis, prognosis, and therapeutic interventions in patients with DOCs. It provides a promising framework in which to integrate different techniques at various spatiotemporal scales, and to merge fragmented findings into a uniform research framework [2]. In this issue, Song *et al.* present a comprehensive review of brain network studies in chronic DOCs with positron emission tomography, functional magnetic resonance imaging (fMRI), functional near-infrared spectroscopy (fNIRS), electrophysiology, and diffusion magnetic resonance imaging (dMRI). An informative perspective on future research directions is also introduced [3]. The Brainnetome can be divided into anatomical and functional components. Diffusion tensor imaging (DTI) is an *in-vivo* dMRI technique for studying the anatomical Brainnetome on the macroscale. Wu *et al.* studied white-matter deficits underlying the consciousness level in patients with DOCs using DTI and discuss the relationship between DTI metrics and clinical measures of the level of consciousness [4]. The functional Brainnetome can be studied with functional brain imaging techniques such as fMRI, EEG/MEG, and fNIRS. Chen *et al.* discuss how the effective connections between various regions differ between individuals with fMRI and a spectral dynamic causal model, and the performance of effective connections in predicting the clinical scores of DOC patients with the Brainnetome-based predictive model [5].

The current diagnosis of DOCs is based on the behavioral responses to commands. It is a major challenge to develop quantitative biomarkers based on neuroimaging and other techniques. In this issue, Tang *et al.* explore the proteomic profile of tears from patients in a traumatic vegetative state and identify potential diagnostic markers using tears – a body fluid that can be collected non-invasively [6]. Zou *et al.* present information on this line of research [7]. The task paradigms are important for the assessment of DOCs. Zhou *et al.* demonstrate that a light is more effective than a finger to trigger a startle blink in

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DOC patients [8]. Prognostication is a fundamental concern for DOC patients, as treatment, rehabilitation therapy, and even ethical decisions depend on this information. It is urgent to develop objective and quantitative measures for the prognosis of DOCs. In this issue, You *et al.* evaluate the predictive value of amplitude-integrated electroencephalography for neurological outcomes in coma patients [9].

So far, evidence-based guidelines on the treatment of DOC patients are rare. Neuromodulation techniques are a potential treatment. In this issue, Xia *et al.* review the current state of neuromodulation therapies that could be used to treat DOC patients [10]. Li *et al.* investigate the effectiveness of habit stimulation in DOC patients with electroencephalography [11]. Wang *et al.* use an oddball paradigm with two types of frequency-deviant stimuli to elicit mismatch negativity in DOC patients diagnosed using the JFK Coma Recovery Scale-Revised [12]. On the one hand, it is very important to quantitatively assess the effectiveness of a neuromodulation method. For example, spinal cord stimulation (SCS) is a promising technique for treating DOCs, but the differences between the effects of different SCS frequencies are unclear. To address this issue, Si and co-authors use functional near-infrared spectroscopy to measure the hemodynamic responses of DOC patients to different SCS frequencies and develop a new quantitative method to evaluate the outcomes of using different SCS frequencies [13].

Brain-computer interfaces (BCIs) have been used for the clinical assessment of DOCs and other disorders of neural systems because they directly detect the responses of such systems to an external stimulus in the absence of behavioral expression. Xiao *et al.* present an electroencephalography-based BCI system to assist the assessment of visual fixation in DOC patients, an item in the visual function subscale of the Coma Recovery Scale-Revised. They also demonstrate the effective performance of the system on 15 patients with DOCs [14].

Despite many advances in the last decade, many challenges for the diagnosis, prognosis, treatment, and rehabilitation of DOCs need to be addressed. For instance, progressive brain atrophy may occur in DOC patients, so techniques for the accurate registration and localization of brain regions are required, given that local information is indispensable for the analysis of this disorder. Second, finer and individualized brain parcellation and the brainnetome atlas generated on the basis of fiber orientation may be essential for the identification of consciousness-related subdivisions and for the development of more accurate interventions for DOC patients [15]. In addition, diagnostic and prognostic models must be validated in independent clinical centers with larger numbers of patients to enable generalization in clinical environments. It should also be noted that biomarker standards based on the physiological disturbances and the circuit/network differences in DOC studies are urgently needed. This issue contains two reviews that discuss future research directions of DOC studies [1, 3]. In parallel, new neuromodulation therapies are required for further validation in a much larger cohort.

Consciousness comes from the brain. The human brain can be studied as a hierarchy of distinct but tightly-integrated levels of organization: from gene, protein, synapse, neuron, and neural circuit, to brain area, pathway, and the whole brain. More and more evidence suggests that combinations of different technologies and the integration of information from different levels can generate more than simply pooling the findings from a single technology or level. We believe that the convergence of diverse disciplines, especially biology, medicine, and informatics, will deepen basic research on DOCs and finally lead to changes in clinical practice.

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