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RESEARCH HIGHLIGHT

A Novel Prognostic Approach to Predict Recovery in Patients with Chronic Disorders of Consciousness

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Severe brain injury can lead to acute or chronic disorders of consciousness (DOC), and the latter represents a more critical challenge in diagnosis and management. For most chronic unconsciousness survivors with preserved sleep-wake cycles, including vegetative state (VS) and minimally conscious state (MCS), levels of consciousness are commonly monitored and determined based on behavioral evidence. VS, also termed unresponsive wakefulness syndrome (UWS), is characterized by complete absence of awareness and may be associated with poor recovery, while MCS exhibit discernible behavioral signs of environmental or self- awareness [1]. Since nearly 40% patients in MCS are initially misdiagnosed as VS/UWS due to the limitation of the existing diagnostic criterion, it is therefore necessary to define the accurate diagnostic and prognostic categorization for long-term outcome [2].

Chronic disorders of consciousness are mainly caused by traumatic or vascular brain injury, with a VS prevalence of 50000-70000 and a ten-fold greater prevalence of MCS in China. Chinese scientific organizations and investigators have become increasingly interested in characterizing patients with chronic disorders of consciousness with an emphasis on diagnosis, prognosis, therapy and rehabilitation since 1990s [3]. In the past few decades, structural and functional neuroimaging techniques have gained considerable attention by Chinese clinical and research centers.

A recent study by Song *et al.* involved three datasets from two medical centers in China, and included 112 patients with chronic DOC as well as 40 healthy participants [4]. The authors developed a novel, computational model to predict the one-year outcome of patients with chronic DOC. Compared with the previous studies using single-domain prognostic models [5], it was the first time to introduce a multi-domain prognostic model, which combined resting state functional MRI with three clinical characteristics. More importantly, the method predicted favorable or unfavorable outcome in patients with chronic disorders of consciousness at single-individual level automatically and objectively, providing new clues for disease management and therapeutic strategies. Unfortunately, although this prognostic model successfully identified nine patients with potentially favorable outcome, three of them did not regain consciousness. A larger cohort with additional variables associated with the outcome is needed to validate and optimize this model in the future.

A total of 22 regions of interest (ROI) as well as six brain networks including the default mode network (DMN), the executive control network (ECN),the salience network (SN), the sensorimotor network (SMN), the auditory network (AN) and the visual network (VN), were extracted and transformed into the imaging features. In addition, the cause of the patients' injury, their age at the time of injury, and how long they have had impaired consciousness were three clinical features. Instead of predicting diagnosis, the study used the outcome of the DOC patient as a target for regression and classification. The result suggested that the combination model achieves a higher prognostic value than any single-domain methods. In addition, connection features of anterior medial prefrontal cortex (aMPFC) and posterior cingulate cortex/precuneus (PCC) in DMN were observed significantly correlated to the behavioral performance 12 months later. Existing evidence suggested that DMN functional

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connectivity is proportional to the level of consciousness, which was also thought to correlate with self-referential processing in patients with chronic disorders of consciousness [6]. Interestingly, the functional connectivity between the dorsal medial prefrontal cortex (DMPFC) in ECN and aMPFC in DMN showed the maximum sMC F-value. Given that the DMN is associated with internally oriented conscious mentation, while ECN is more related to externally oriented processes [7], it may be speculated as a reliable predictor for the long-term outcome of the patients with chronic DOC.

With the development of novel imaging and sequencing technologies, an association between brain networks and pathophysiologic changes has been found. To date, there has been a growing number of studies revealing alterations of microstructural, macrostructural, or connectional features in various brain disorders. In an attempt to understand the complex features of consciousness, multiple techniques with different strengths and weaknesses emerge. Stender *et al*. have suggested that PET imaging is a more sensitive and reliable outcome predictor compared with functional MRI [8]. Meanwhile, EEG recordings served as a low-cost, easily repeatable and time-resolved alternative to detect the residual consciousness and the potential to recovery [9]. Moreover, functional and anatomical neuroimaging studies on brain networks of patients with chronic DOC help to understand the underlying processes of unconsciousness and human brain, thereby deepening the understanding of the disease, and even improving the clinical applications including diagnosis, prognosis, and therapeutic effects. It is well expected that the integration of multi-modal data may achieve more satisfactory performance.

The "omics" technologies, also termed as "systems biology", aim to integrate genomics, transcriptomics, proteomics, metabolomics, and other system-level findings and provide a global description of changes in different states of disease. The highly convergence of diverse disciplines, especially clinical assessment, neurocomputing, bioinformatics and medical imaging, is dramatically changing the field of brain function. The development of computational methods has revolutionized our ability to calculate, analyze and interpret the clinical data, and promoted the interdisciplinary research in neural mechanisms of consciousness and related disorders. The Brainnetome project, an emerging constituent of the "omics" technologies, was launched in China in 2010 and was designed to investigate the hierarchy from genetics to neuronal circuits to behaviors [10]. As a powerful tool for outcome prediction in patients with chronic DOC, Brainnetome poses a challenge and an opportunity for researchers, and ultimately benefits the patients and society.

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