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Association of medial prefrontal cortex connectivity with consciousness level and its outcome in patients with acquired brain injury

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ABSTRACT

Medial prefrontal cortex (mPFC) is usually known for participating in virtually all self related processing. However, few have investigated the role of mPFC in modulating conscious awareness. This study aimed to depict the relationship between the mPFC connectivity and the severity and outcome of the disorders of consciousness (DOC) among patients with acquired brain injury. Thirty-four patients with DOC (17 in a minimally conscious state and 17 in an unresponsive wakefulness syndrome/vegetative state) and 11 healthy controls were recruited, underwent clinical assessment and resting-state functional MRI scan, and were further followed up to evaluate recovery outcome using the Glasgow Outcome Scale. The mPFC connectivity was then analyzed, by comparing DOC patients to healthy controls at baseline, and by comparing "recovered consciousness" and "non-recovered consciousness" patients at follow-up, as identified by graph theory. As a result, enhanced mPFC connectivity against weakened posteromedial cortex connectivity was observed in a minimally conscious state, not in an unresponsive wakefulness syndrome/vegetative state. Besides, increased mPFC connectivity was significantly associated with consciousness recovery. In conclusion, the mPFC connectivity could possibly serve as a mark to track the severity and outcome of DOC.

1. Introduction

Recent advances in the field of disorders of consciousness (DOC) have highlighted the spectrum following coma and its graded nosology, including coma, unresponsive wakefulness syndrome/vegetative state (UWS/VS) [1], minimally conscious state (MCS) [2] and confusional state [3,2]. Differentiating between the various states of DOC is challenging [4]. With regard to treatment strategies and medical-legal decision making, it is centrally important to determine the consciousness state and recovery potential of acquired brain-injured patients at early stage, and to accurately predict whether those patients would regain consciousness and functional independence. However, it remains a big challenge.

Recently, significant advances have been made by several neurophysiologic and functional imaging studies to resolve these challenges. It seems that functional brain mapping is a valuable paradigm to characterize severe brain injury. Inferences made from functional activation studies are employed to assess consciousness and communication [5,6]. Furthermore, resting-state functional MRI (rs-fMRI) has emerged as a promising tool to investigate consciousness, as it requires no task-based fMRI paradigms, and is thus easily performed; it also shows a spatiotemporal correlation within functional networks during rest [7].

Meanwhile, it was reported that the prefrontal cortex (PFC) is the core of the brain. It participates in the humans mental activities, especially in cognitive processing. Recently, with the development of cognitive neuroscience and neuroimaging, researchers have made obvious progress on study in the PFC and further refined different functions which different subregions of the medial prefrontal cortex (mPFC) serve as in advance human cognition. Studies have shown that the mPFC participated in virtually all self related processing: affecting human identity, altering attentional processes, decision-making, goal-directed behaviour and working memory [8–11]. Furthermore, it was reported that the progressive reduction in astrocytic branching and domain in the mPFC can account for the integrative dysfunction leading to the cognitive deficits and memory disturbances observed in Alzheimer's disease (AD) [12]. Actually, the pattern of increased connectivity of the mPFC has also been reported by previous study on AD [13], as

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mPFC has a role of compensatory. Alterations in the mPFC are even more important for frontotemporal dementia [14–16]. Also, the mPFC is one component of DMN, which is indicative of internally oriented awareness and spontaneous cognition [17]. It has been reported that functional connectivity between PCC and mPFC may predict patient outcome from coma [18]. However, the role that mPFC plays in modulating conscious awareness is incompletely understood; furthermore, how mPFC changes as the consciousness progresses is not determined clearly yet.

Therefore, our first aim of the current study is to compute the mPFC in a cohort of patients with DOC, including MCS and UWS/VS, and healthy controls, thereby tracking the neural changes of mPFC between patients and healthy controls. Secondly, we aim to relate alteration of the mPFC integrity to consciousness recovery, so as to allow a much deeper understanding of the mechanisms underlying consciousness recovery and promote early prognosis of recovery outcome following by in patients with acquired brain injury. We further hypothesize that the neural trajectories of mPFC was correlated with consciousness progress.

2. Materials and methods

2.1. Participants

Forty brain-injured patients and 11 healthy volunteers participated in the experiment. All the patients were from the Department of Rehabilitation in the Hangzhou Hospital of Zhejiang (CAPR), Hangzhou, China. None of the controls had a history of psychiatric or neurological illness, psychoactive drug consumption, or drug or alcohol abuse. Six patients with excessive head motion during imaging or excessive deformation in brain structure were removed from the analysis, including M001, M006, M018, V005, V008, and V020. The remaining 34 patients (22 male; mean age, 45.0 ± 17.8 years) and 11 control subjects (6 male; mean age, 46.0 ± 18.6 years) were included in the analysis. The 34 patients had recovered from coma at baseline. They were categorized into two subgroups according to the internationally established criteria for MCS and UWS/VS [3,2]: (1) MCS subgroup (17 patients; 12 male; mean age, 41.8 ± 19.8 years); (2) UWS/VS subgroup (17 patients; 10 male; mean age, 48.1 ± 15.5 years).

We performed the rs-fMRI scan and consciousness assessments of patients under stable conditions after the brain injury, with the rs-fMRI scan performed between six and 228 days (72.4 ± 52.2 days) after brain injury. Consciousness level was assessed using (GCS) and the Coma Recovery Scale-Revised (CRS-R) on the day of the rs-fMRI scan. Recovery outcome was evaluated by the Glasgow Outcome Scale (GOS) at three months after the rs-fMRI scan. The GCS score tested eye opening, verbal response, and motor function, respectively, with the total score ranging from three to 15; the CRS-R score tested auditory function, visual function, motor function, oro-motor/verbal function, communication, and arousal, with a score ranging from zero to 23. The CRS-R movement subscale ranged from zero to 6. The GOS score ranged from one to five, with a score of no less than three regarded as having recovered consciousness, and less than three as non-recovered consciousness (1 = dead; 2 = vegetative state/severe disability; 3 = able to follow commands but unable to live independently/-moderate disability; 4 = able to live independently but unable to return to work or school; 5 = able to return to work or school/good recovery).

The study was approved by the Ethics Committee of the First Affiliated Hospital, School of Medicine, Zhejiang University, and written informed consent was obtained from healthy participants and the legally authorized representative of the patients.

2.2. MRI imaging

MRI images of the subjects were obtained on a Magnetom Essenza Electric 1.5 Tesla scanner (Siemens, Germany) with a homogeneous birdcage head coil. Subjects lay supine with their heads snugly fixed by a belt and foam pads to minimize head motion. High-resolution T1-weighted images covering the whole brain were acquired using a T1-weighted 3D magnetization-prepared rapid gradient echo sequence: repetition time (TR) = 2000 ms, echo time (TE) = 5.18 ms, flip angle (FA) = 15°, acquisition matrix = 256 × 256, field of view (FOV) = 240 × 240 mm, thickness = 1.0 mm, gap = 0.5 mm. T2*-weighted functional images were obtained with a gradient-echo echo-planar imaging sequence using axial slice orientation and covering the whole brain (TR = 2000 ms, TE = 40 ms; FA = 90°, acquisition matrix = 64 × 64, FOV = 240 × 240 mm, thickness = 5.0 mm, gap = 1 mm). This acquisition sequence generated 240 volumes in 8 min. All subjects were instructed to keep their eyes closed during scanning.

2.3. Image pre-processing

FMRI images were pre-processed using Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm/) and the rs-fMRI Data Analysis Toolkit (REST 2.3, http://resting-fmri.sourceforge.net/). The first ten volumes of the functional images were discarded for T1 equilibrium and the participants' adaptation to the scanning conditions. Slice timing and head motion correction were then performed on the remaining images. Participants were excluded from the study after displaying head motion more than 2.0 mm maximum displacement in any direction (x, y, or z) or 2.0 degrees of any angular motion. The resulting images were resampling to 3 × 3 × 3 mm voxels and smoothed with a Gaussian kernel of 4 × 4 × 4 mm FWHM. Finally, detrending was applied to remove the linear trend of time courses, and a temporally band-pass filter was conducted to ensure the residual blood oxygen level-dependent time series was over a low-frequency fluctuation between 0.01 and 0.08 Hz.

2.4. Defining regions of interest (ROIs)

MPFC is one important component of the DMN. Considering the DMN network has reduced activity in brain areas with the patients of DOC [19–21], and the DMN connectivity is correlated with the severity of consciousness impairment [22,19,23,21], relates to the recovery outcome of DOC [24,23,25,18,26]. So other components were also selected as seeds, like posteromedial cortex, lateral parietotemporal cortex, as well as the medial temporal lobe, the main hubs of which are within the mPFC and along the posterior midline including posterior cingulate cortex/precuneus (PCC/PCU) [27]. The brainstem areas, the thalamus, and the cerebellum have been identified as connected to the DMN during recovery [28], so these must also be taken into consideration. We created, with reference to the literature, the following seeds at the fingerprints from the peak Montreal Neurological Institute (MNI) coordinates of the ROIs [29][coordinates in MNI space, centered at x, y and z]: PCC/PCU [0 −52 27], mPFC [−1 54 27], left lateral parietal cortex (LPC_L) [-46 −66 30], right lateral parietal cortex (LPC_R) [49 −63 33], left inferior temporal cortex (ITC_L) [-61 −24 −9], right inferior temporal cortex (ITC_R) [58 −24 −9]), left cerebellum (Cb_L) [-25 −81 −33], right cerebellum (Cb_R) [25 −81v −33], thalamus (Th) [0 −12 9], and brainstem (Bst) [12 −24 −24], in Fig. 1. Second, in order to exclude the influence of skull defects following brain injury and brain surgery and to guarantee the structural integrity of these seeds, we performed visual assessments of T1 imaging