



Research article

Alteration in ventral tegmental area and default mode network interplay and prediction of coma recovery in patients with sTBI

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ABSTRACT

Purpose: To investigate the role of VTA and DMN in modulating human consciousness in patient with sTBI.

Methods: We mapped an atlas of VTA in the brainstem and a total of 19 region of interests in the ventral and dorsal DMN onto functional magnetic resonance imaging in 28 patients with sTBI and 28 healthy controls. We assessed the functional connectivity alteration in subcortical VTA and cortical DMN nodes in patients of coma. We evaluated the spatially distribution of FC alteration in VTA and DMN nodes after sTBI and evaluated their predictive value for coma recovery.

Results: There was a decrease in FC between VTA and DMN in patients compared to controls. After decomposition, the FC between VTA and 10 DMN nodes were decreased whereas the FC within 2 DMN nodes were increased in patients with acute coma. The FC alteration in DMN nodes provided useful information for the early prediction of 6-month coma recovery in patients with sTBI.

Conclusions: We provide initial evidence for the decreased FC between VTA and massive DMN nodes in patients with coma in acute phase of sTBI. We found that the FC alteration within DMN is more useful than the FC alteration between VTA and DMN for predicting coma recovery in patients with sTBI. VTA and DMN connectivity mapping provides an opportunity to advance the cortical-subcortical mechanism of human consciousness.

1. Introduction

Coma is believed to be result from structural brain lesions and diffuse brain dysfunction in patients with severe traumatic brain injury (sTBI) [1]. Up till now, coma has been proven to be related to the disruption across corticocortical, thalamocortical and thalamostriatal connections [2,3]. Moreover, traumatic coma is thought to be caused by the disruption of ascending arousal network, especially a pathway between brainstem tegmentum to hypothalamus and thalamus [4]. Despite the connectivity diversity, a common pathophysiological mechanism of coma is the widespread decreasing of excitatory synaptic activity across cerebral cortex [3].

In the two-dimensional representation of consciousness, coma is supposed to be the common defect of awareness and wakefulness [5]. In the past, decades of preclinical studies indicated that subcortical ventral tegmental area (VTA) of midbrain has a central role in

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regulating awareness (behavior and cognition) [6]; Meanwhile, animal studies demonstrated that the VTA has an essential role in promoting wakefulness through projections to subcortical regions [7]. However, the regulatory effect of VTA in human coma remains elusive because of cross-species differences. Recently, a landmark study suggested that the functional connectivity (FC) decreased between VTA and precuneus and posterior cingulate (PCu/PCC) is associated with unconsciousness produced by propofol sedation and sTBI [8]. To our knowledge, PCu/PCC is a well-established “hub node” of the cortical default mode network (DMN), in which the FC will compensatory increase in patients after sTBI [9,10]. Although these findings support the VTA–PCu/PCC connectivity in modulating human consciousness, a direct “one-to-many” relationship between VTA and broader DMN nodes have not been investigated.

Furthermore, in clinical practice, early prediction of the recovery of consciousness in patients with traumatic coma has become an urgent and indispensable issue. In general, most of the sTBI patients will not recover from the coma in the acute phase, and the coma will last until the rehabilitation phase [11]. Without knowing whether a patient will recover from coma, many hopeless family members voluntarily withdraw life-supporting treatment in the acute phase. It has been reported that a decision of active withdrawal account for up to 68% in-hospital mortality in patient with sTBI [12]. Accordingly, identifying the coma recovery trajectory in the acute phase of sTBI may inform acute decision-making, that is, rationality is warranted in consideration of withholding life-sustaining therapies [13].

In the present observational study, we hypothesized that: 1) sTBI results in abnormalities of FC between VTA and broader DMN nodes; 2) these alterations are compatible with the coma in the acute phase; and 3) early detection of FC alteration within VTA and DMN could inform coma recovery in 6-month after sTBI.

2. Methods

2.1. Patients with sTBI and healthy controls

This prospective observational study was performed in June 2018 to June 2021. Patients who met the following criteria were included: 1) Age 18–80 years old; 2) closed craniocerebral injury with admission Glasgow Coma Scale (GCS) scores ≤ 8 [14]; 3) with no eye-opening or verbal response for 24 h on evaluation unconfounded by drug sedation [14]. These patients were excluded: 1) unstable vital signs; 2) with multiple injuries; 3) history of neurological and/or psychiatric; 5) abuse of alcohol, and/or drugs; 6) with contraindications for magnetic resonance imaging (MRI); 7) with disability before brain trauma; 8) left-handedness.

During the investigation period, 2 patients were excluded because of motion artifacts identified by an investigator blinded to the clinical data (C.-X.X.). We eventually retained 28 patients with sTBI [19 male and 9 female, age 58.00 ± 15.39 years (mean \pm SD)] (Table 1). In addition, we also recruited 28 age and gender-matched healthy controls. For the sTBI patients, family members provided written informed consent in accordance with a research protocol approved by Local Ethics Review Board. For the healthy controls, informed consent was signed by themselves.

2.2. Clinical and outcome assessments

In this study, we defined the awaken from coma as the patients present with behavioral sign of responsiveness, such as eye-gaze tracking, stimuli localization or command-following. Notably, the former two represent emergence from coma to the minimally conscious state [3], and the latter one is a commonly used measure responsiveness in patients with sTBI [15]. We defined a recovery of consciousness (wake) as any emergence of the abovementioned symptoms within 6-month after injury. Meanwhile, we also assessed outcome using the Glasgow Outcome Scale-Extended (GOS-E). The demographic and clinical assessment were collected at the time of enrolment and at 6-month follow-up, and all participants were grouped according to different goal-settings.

2.3. Demographic and clinical data analyses

Two independent t-tests and chi-square tests (only for gender) were performed to compare the demographic and clinical data from the sub-groups (healthy controls vs. coma patients; wake group vs. coma group) (SPSS 26.0; SPSS, Inc., Chicago, IL, United States). The significance level was set at $p < 0.05$. The demographics and clinical measurements of all participants in this study are available in Table 1.

Table 1

Baseline features of this study participants.

Term	Healthy controls	Coma patients	Wake group	Coma group	P value
Age, (Mean \pm SD)	55.21 \pm 18.09	58.00 \pm 15.39	52.23 \pm 17.22	59.38 \pm 15.98	0.54 ^a ; 0.36 ^b
Gender, male (%)	18 (64.3)	19 (67.9)	7 (87.5)	8 (61.5)	0.78 ^a ; 0.20 ^b
Right-handed, N (%)	28 (100.0)	28 (100.0)	13 (100.0)	8 (100.0)	–
aGCS, (Mean \pm SD)	–	5.00 \pm 2.45	5.85 \pm 2.38	2.88 \pm 1.36	0.002 ^b
GOS-E, (Mean \pm SD)	–	3.00 \pm 1.93	4.69 \pm 1.49	2.00 \pm 0.00	<0.001 ^b

aGCS: admission Glasgow coma score; GOS-E: Glasgow outcome score expansion (a. healthy controls vs. coma patients; b. wake group vs. coma group).

2.4. Imaging data acquisition

Functional MRI (fMRI) was performed as soon as a sTBI patient was vital sign stable for transport to the MRI scanner, which has been determined by the treating neurosurgeons about 14 days after admission. The blood oxygen level dependent fMRI data were acquired with a 3.0 T, 8-channel, Head coil MRI scanner (Discovery MR750; GE Medical Systems, Milwaukee, WI, USA) with gradient echo planar (percent phase field view = 100, flip angle = 90° , TE = 30 ms, TR = 2000 ms, FOV = 300×300 mm, matrix = 64×64 , thickness = 3.5 mm, spacing between slices = 4.2 mm, and slices = 33, 8 min).

High-spatial resolution 3D T1-weighted image was acquired covering the whole brain (TE = 3.18 ms, TR = 8.16 ms, FOV = 256×256 mm, flip angle = 12° , matrix = 256×256 , slice thickness = 1 mm, interslice gap = 0 mm, and 168 slices) for registration and anatomical location purposes. During the fMRI scanning, the sTBI patients were lay supine with the head firmly fixed by a coil and sponge to minimize head motion. The MRI compatible monitors were used to monitor vital signs of all participants. If abnormal, stop scanning immediately. Meanwhile, fMRI data of healthy control patients were acquired with the same scanning procedures.

2.5. fMRI data pre-processing

All fMRI data pre-processing were performed on the basis of MATLAB 2016b (MathWorks, Natick, MA, USA). The DPABI toolbox (<http://rfmri.org/DPABI>) was used for the procedure, which included: remove first (10 time series), slice timing, segment, head-motion correction, and spatial normalization. Significantly, the patients with sTBI were inevitably restless in the acute phase, which had been eliminated as follows: the participants with more than 2.0 mm maximum translation and 2° of rotation (x, y, and z directions) were ruled out, and a higher-order framework (Friston 24 head motion parameters model) 16 was applied to regress out head motion effects. After that, linear regression was used to remove spurious covariates along with temporal derivatives (such as white matter, cerebrospinal fluid signals). Then, the low-frequency drift, physiologically high-frequency (respiratory and cardiac noise), and time-series linear detrending have been reducing through bandpass filtration (0.01–0.1 Hz) and linearly detrended. In addition, the fMRI images were normalized to the Montreal Neurological Institute (MNI) template and spatially re-sampled at a resolution of $3 \times 3 \times 3$ mm³ space. Finally, the data were smoothed using a Gaussian kernel of $4 \times 4 \times 4$ mm³ full width at half-maximum (FWHM).

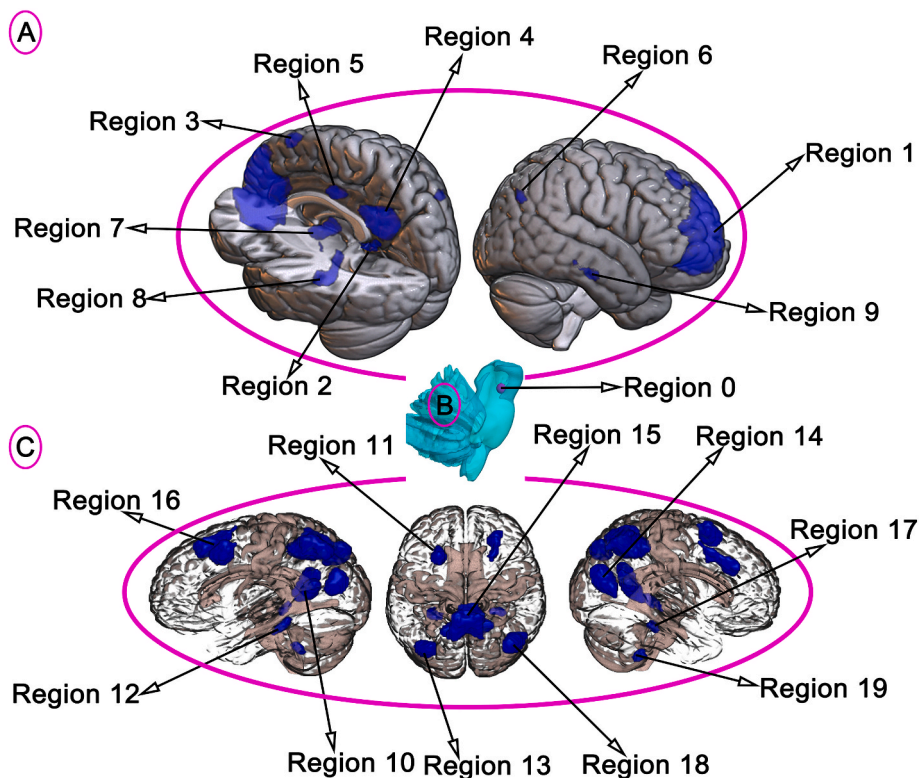


Fig. 1. Schematic visualization of regions of interest [A. dorsal default mode network; B. ventral tegmental area; C. ventral default mode network (regions 0 to 19 are ventral tegmental area, medial frontal gyrus, angular gyrus, superior frontal gyrus, posterior cingulate, median cingulate and paracingulate gyri, supramarginal gyrus, thalamus, parahippocampal gyrus, parahippocampal gyrus, posterior cingulate, superior frontal gyrus, fusiform gyrus, middle occipital gyrus, posterior cingulate, superior parietal lobule, superior frontal gyrus, fusiform gyrus, middle occipital gyrus and cerebellar tonsil, respectively)].

2.6. Delineate regions of interest of VTA and DMN

Regions of interest (ROIs) were defined using DPABI toolbox. The peak point for the VTA in standardized MNI space were defined according to a procedure previously outlined by Chen et al. (MNI coordinate: 0, -22, -12) [16]. We created a 3-mm sphere at the peak point and applied this for further time-series extraction [17]. Meanwhile, we defined the 19 ROIs in both dorsal (ROIs = 9) and ventral DMN (ROIs = 10) with reference to the spatial maps provided by Stanford's Functional Imaging in Neuropsychiatric Disorders (FIND) Laboratory [18]. Detailed coordinates of VTA and DMN in MNI standard space are available in the Supplement Table 1, and Fig. 1A–C that illustrate the definition of the ROIs on VTA and DMN in this analysis.

2.7. fMRI data analysis

In this study, we utilized a ROI-wise analysis to investigate differences of the FC in the VTA and DMN. Protocol was performed sequentially in two steps. First, the whole DMN and spherical VTA masks were used to extract DMN and VTA related time-series, respectively in each subject (to investigate the FC difference of VTA and whole DMN). Meanwhile, we extracted the time-series from each ROI listed above (Supplement Table 1 and Fig. 1 A–C) and constructed the FC matrix base on ROI pairs (that is, paired FC). Thus, a 20×20 symmetric FC matrix was yielded for each subject. These FCs were constructed by Pearson correlations with time series and the results of correlation coefficients were Fisher transformed to Z values to increase normality.

The two-sample t-tests was performed to examine the differences in the FC of VTA to whole-DMN and the paired FC between the coma patients and the healthy controls. In addition, the two-sample t-tests was applied to analysis the differences of each paired FC between the wake and coma groups. The finding was corrected for multiple comparisons by the false discovery rate (FDR) approach (with the exception of VTA to whole-DMN) (<https://cran.r-project.org/web/packages/NBR/index.html>). The significance level was set at $P < 0.05$.

2.8. Coma recovery prediction analysis

We proposed that whether the altered FC patterns in VTA and DMN could be used for predicting coma recovery in patients with sTBI. Here, the receiver operating characteristic (ROC) curves were constructed to verify the predictive ability of the FC pairs. The area under the curve (AUC) was used to measure prognosis-prediction accuracy. An AUC of 1 indicated perfect discrimination, whereas an AUC of 0.5 implied random classification.

3. Results

3.1. Decreasing in the interplay between VTA and whole-DMN in coma

For ROI-wise connectivity, compared with the healthy controls, FC between VTA (Fig. 2B) and whole-DMN (Fig. 2A) exhibited significantly decreased in patients with sTBI who present with acute coma ($p < 0.05$, FDR corrected) (Fig. 2C).

4. Alteration function connectivity in VTA and DMN after sTBI

As illustrated in Fig. 3A and B, both increased and decreased FCs could be found in patients who present acute coma after sTBI. Specifically, FCs of VTA-DMN (10 ROI pairs) and mostly within DMN (33 ROI pairs) were decreased, while partially FCs within DMN (1 ROI pair) was increased (detailed coordinate information of ROIs are available in Supplement Table 1). For decreased paired FCs between VTA and DMN, the VTA to right superior frontal gyrus indicated the highest difference in coma patients and health controls

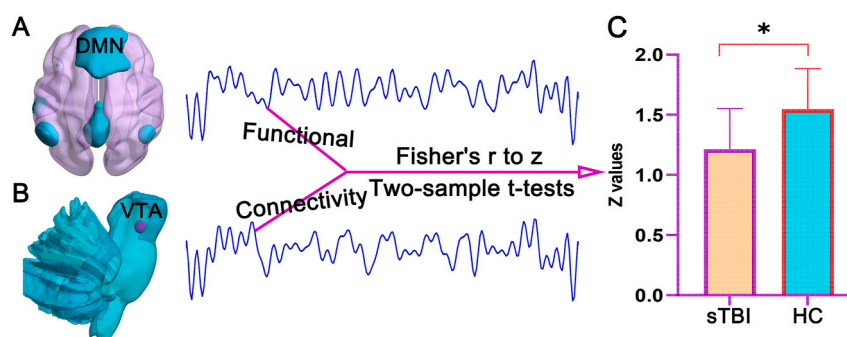


Fig. 2. Difference between groups of global functional connectivity in ventral tegmental area and default mode network [A. schematic diagram of ventral tegmental area; B. map of default mode network; C. comparison of functional connectivity indicated that the difference was statistically significant between severe traumatic brain injury and health controls. (VTA: ventral tegmental area; DMN: default mode network; sTBI: severe traumatic brain injury; HC: health controls; *represents $P < 0.05$)].

(Fig. 3C). Moreover, for all decreased paired FCs within DMN, the left parahippocampa gyrus to right parahippocampa gyrus, left fusiform gyrus to right parahippocampa gyrus, left posterior cingulate to right posterior cingulate, right superior frontal gyrus to left fusiform gyrus, right fusiform gyrus to left fusiform gyrus, and right superior frontal gyrus to left fusiform gyrus demonstrated the highest between-group statistical difference (Fig. 3D).

5. Differentiation of FC alteration in coma and awake

We further investigated whether the FC alteration of VTA and DMN were compatible with the disappearance or existence of human consciousness. After excluding 7 patients who died during follow-up, we then divided the remaining 21 patients into coma (n = 8) and awake (n = 13) groups according to their responsiveness at 6-month (as mentioned in methods). Interestingly, the findings indicated that 12 paired FC located in the DMN regions showed significant differences between the coma and awake groups (Fig. 4A–E). However, we did not find the statistically difference of FC in the ROI pairs that locate between VTA and DMN nodes between groups (Fig. 4A–E).

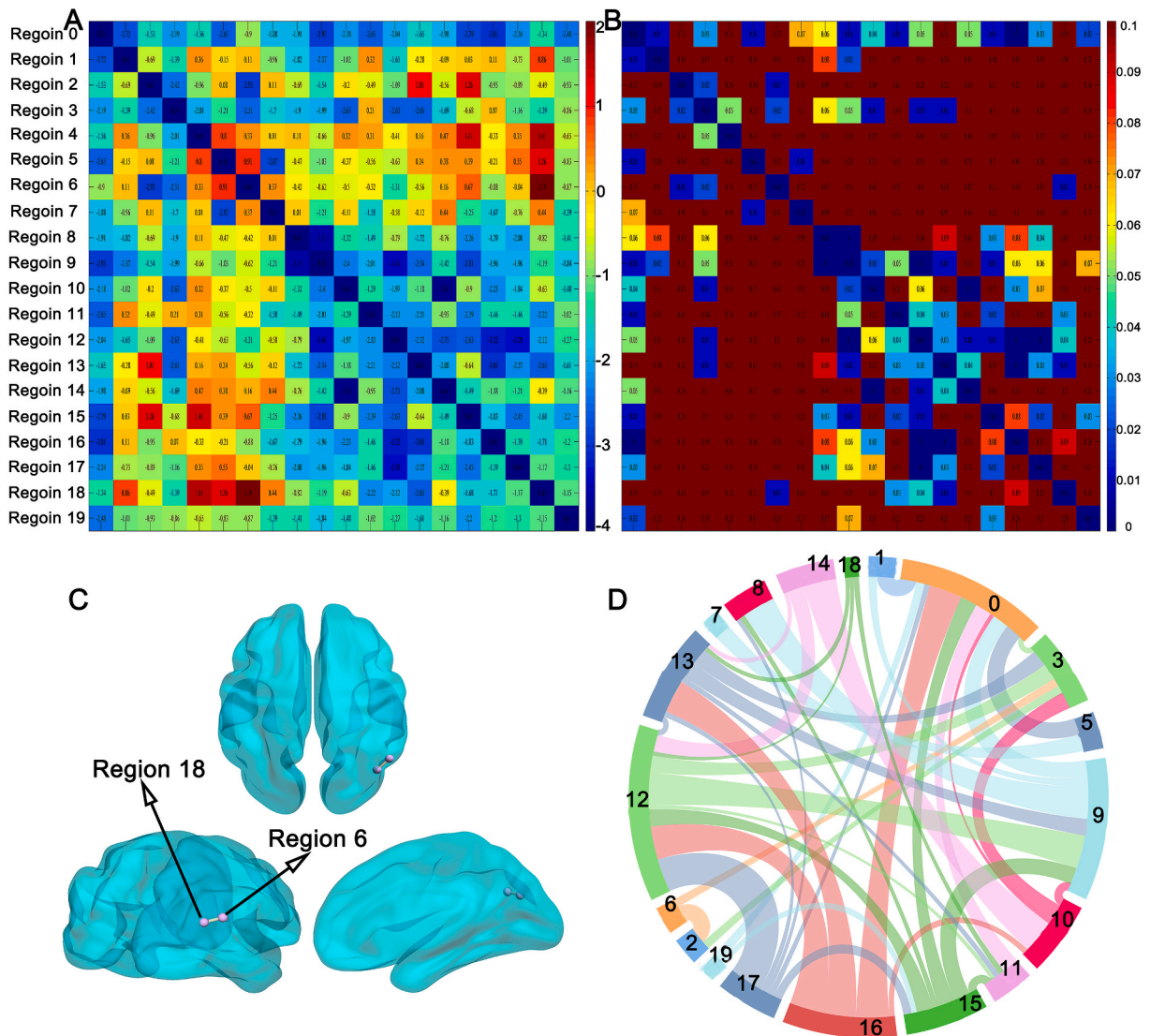


Fig. 3. Difference of the paired functional connectivity between severe traumatic brain injury and health controls [A. T-value matrix - degree of difference in functional connectivity; B. statistical P-value matrix; C. increased of functional connectivity into paired brain areas; D. decreased of functional connectivity into paired regions of interest (regions 0 to 19 represent ventral tegmental area, medial frontal gyrus, angular gyrus, superior frontal gyrus, posterior cingulate, median cingulate and paracingulate gyri, supramarginal gyrus, thalamus, parahippocampa gyrus, parahippocampa gyrus, posterior cingulate, superior frontal gyrus, fusiform gyrus, middle occipital gyrus, posterior cingulate, superior parietal lobule, superior frontal gyrus, fusiform gyrus, middle occipital gyrus and cerebellar tonsil, respectively)].

6. Predicting 6-month coma recovery

As we found group differences in FC alterations between the coma and awake groups, we test the role of altered FC in predicting the 6-month coma recovery in patients with sTBI. Our findings suggested that the FC in 12 ROI pairs that locate in DMN nodes were effective (with AUC range from 0.750 to 0.808) in predicting 6-month recovery for traumatic coma patients (Fig. 5A–D). Meanwhile, our results revealed that either in anterior (i.e., prefrontal, anterior cingulate, and orbitofrontal) or in posterior (i.e., parietal, occipital, and lateral temporal) DMN nodes, yielded similar predictive ability for predicting coma recovery. Among which the FC alteration between the left middle occipital gyrus and the right superior marginal gyrus showed the highest predictive ability (detailed AUC of ROI pairs are available in Supplement Table 2).

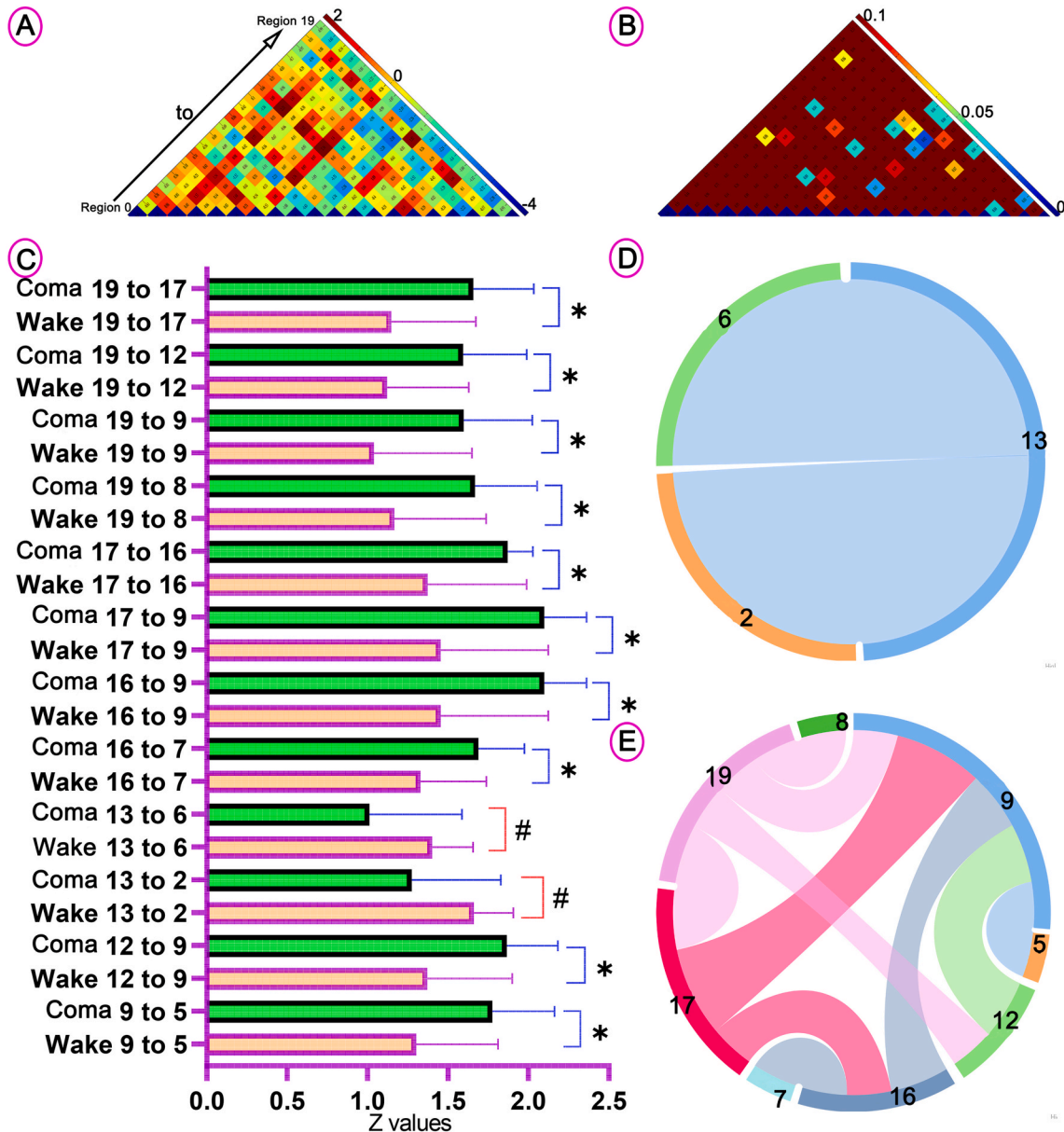


Fig. 4. Between group difference of the paired functional connectivity in patients with wake and coma after 6 months [A. T-value matrix; B. statistical *P*-value matrix; C. quantification analysis of functional connectivity strength, i.e. Z-value comparison between groups; D. increased of functional connectivity into pairwise brain areas; E. decreased of functional connectivity into pairwise regions (regions 0 to 19 are ventral tegmental area, medial frontal gyrus, angular gyrus, superior frontal gyrus, posterior cingulate, median cingulate and paracingulate gyri, supramarginal gyrus, thalamus, parahippocampa gyrus, parahippocampa gyrus, posterior cingulate, superior frontal gyrus, fusiform gyrus, middle occipital gyrus, posterior cingulate, superior parietal lobule, superior frontal gyrus, fusiform gyrus, middle occipital gyrus and cerebellar tonsil, respectively; *represents *P* < 0.05)].

7. Discussion

The significance of this study is that we bridged the gap between subcortical and cortical connections in modulating human consciousness through the ROI-wise FC analysis in the VTA and DMN. We verified the initial hypothesis that traumatic coma was a result from the functional decreased between VTA and broader DMN nodes. Our ROI-wise connectivity findings also added evidence to the traditional theories that broader DMN nodes are involved in coma recovery [3,19].

There is ongoing debate about whether the neural correlates of human consciousness were emerged from bottom-up (i.e., subcortical) or top-down (i.e., cortical) regions [20]. To our best knowledge, severely brainstem lesions can destroy the reticular activating system and result in an immediate coma, and extensively cortex damaged but with relatively spared brainstem can also lead to unconsciousness [21]. This suggests that consciousness is not the result of single brain area activity but the interaction and cooperation activities among massive brain regions. In the present study, we found that there were FC decreased in FC between VTA and 10 DMN nodes whereas increased in 2 nodes and decreased in 33 pairs of nodes within DMN in patients who present acute coma

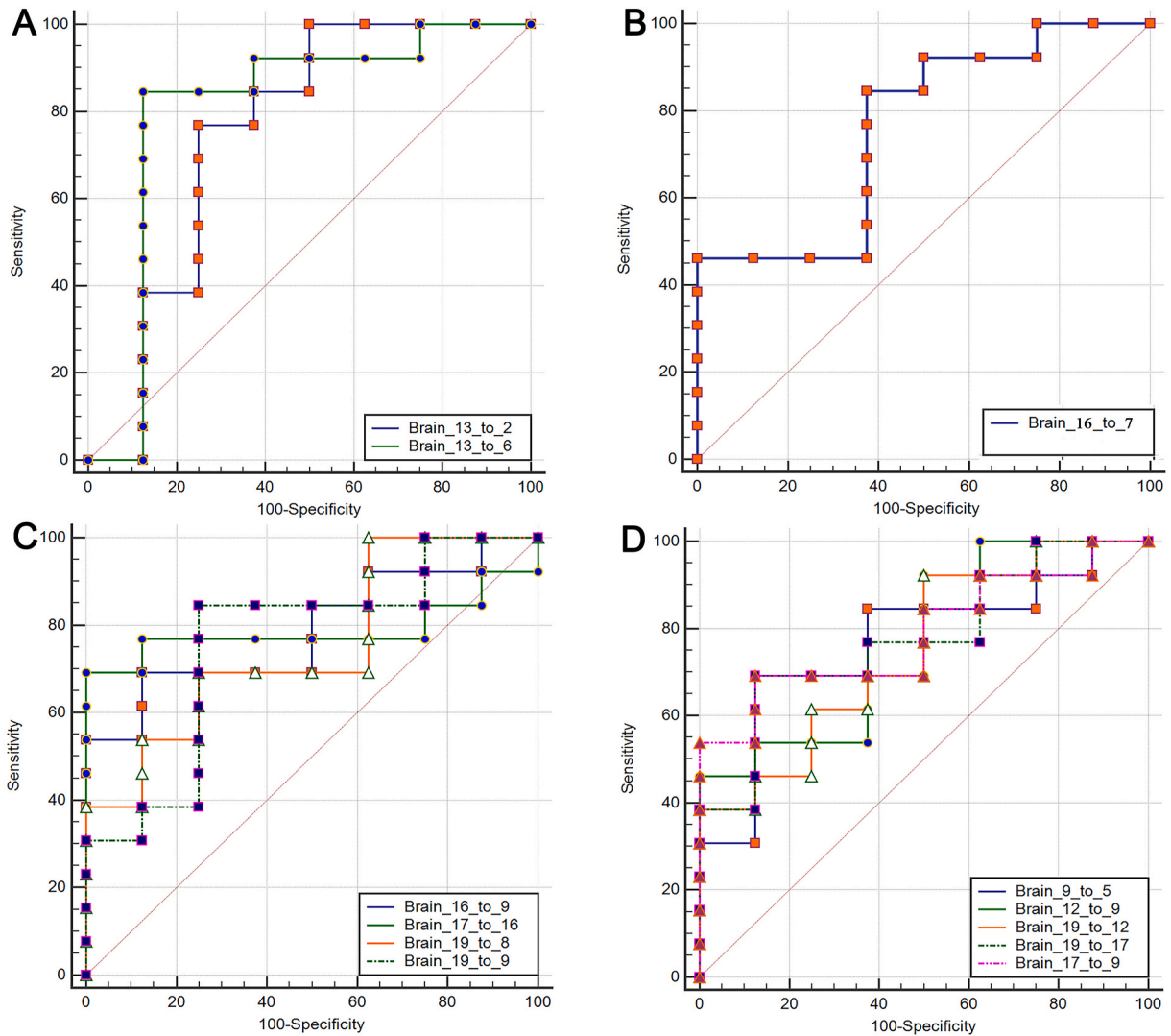


Fig. 5. Functional connectivity strength discriminative ability for coma recovery [A. (regions of interests; Region 13 to 6: functional connectivity strength in left middle occipital gyrus and right supramarginal gyrus); B. (Region 16 to 7: functional connectivity strength in right superior frontal gyrus and thalamus); C. (Region 16 to 9: functional connectivity strength in right superior frontal gyrus and right parahippocampal gyrus; Region 17 to 16: functional connectivity strength in right fusiform gyrus and right superior frontal gyrus; Region 19 to 8: functional connectivity strength in right cerebellar tonsil and left parahippocampal gyrus; Region 19 to 9: functional connectivity strength in right cerebellar tonsil and right parahippocampal gyrus); D. (Region 9 to 5: functional connectivity strength in right parahippocampal gyrus and median paracingulate cingulate gyri; Region 12 to 9: functional connectivity strength in left fusiform gyrus and right parahippocampal gyrus; Region 19 to 12: functional connectivity strength in right cerebellar tonsil and left fusiform gyrus; Region 19 to 17: functional connectivity strength in right cerebellar tonsil and right fusiform gyrus; Region 17 to 9: functional connectivity strength in right fusiform gyrus and right parahippocampal gyrus)].

after sTBI. These findings provide a putative mechanism of traumatic coma, that is, alteration in VTA and DMN interplay originated from reintegration of region connections.

Indeed, the study by Spindler et al. [8] provide convergent evidence that VTA disconnection from the PCu/PCC in human perturbed consciousness. Those findings highlight the importance of the posterior cortex in spurting human consciousness, suggesting that PCu/PCC can not only role as a hub of DMN but also as a hub for subcortical-cortical integration [20]. However, it remains to be determined whether the “front” (i.e., dorsolateral, medial prefrontal, anterior cingulate, and orbitofrontal) or the “back” (i.e., parietal, occipital, and lateral temporal) of the cerebral cortex is more important in supporting consciousness [22]. In the present study, our results indicated that there were decreased FC in VTA to both anterior and posterior DMN nodes in patients who present acute coma, suggesting there was one-to-many relationship between VTA and DMN nodes. Specifically, human consciousness may be derived from the massive subcortical-cortical connectivity between VTA and DMN nodes rather than from a single connectivity (i.e., VTA–PCu/PCC) modulating the DMN broader connectome. Therefore, identifying more VTA-DMN connectivity could advance our understanding of the subcortical-cortical mechanism that contribute to human consciousness.

An unexpected observation in this study was FC alteration within DMN is more useful than the FC alteration between VTA and DMN for predicting 6-month coma recovery in patients with sTBI. Disruptions are more common in the cerebral cortex and limited subcortical areas by sTBI (relatively limited damage to deep subcortical connections). Therefore, over time, deep subcortical connections that were dissociated will effectively re-establish in patients with sTBI. However, communication between widely disrupted cortical regions is not restored in every sTBI patient. Once, the pathways are reestablished in core brain regions of consciousness regulation, including the DMN, would imply potentially promising recovery from traumatic coma. A peculiar phenomenon occurs when humans wake up from non-REM sleep. Despite most subcortical neuroregulatory systems are reduced, participants are reported to be conscious before waking up in more than one-third of instance [23,24]. This means that arousal and perception may be controlled by two interacting consciousness systems. Even so, we should stay conservative in these findings, as follows: 1) the subcortical neurotransmitters signaling may have countervailing influences on the FC alteration, of which dopamine and serotonin signaling have the opposite effects on DMN activity [25]; 2) FC within DMN alone is not sufficient for explaining the mechanisms of coma recovery, and there were dynamic interactions between DMN node and subcortical regions [26,27]. More study is needed to confirm these speculations.

In addition, our results demonstrated that increased FC in the left middle occipital gyrus and the right supramarginal gyrus has the highest predictive ability for coma recovery in patients with sTBI. These findings are in line with a recent FC study in patients with sTBI, that is, patients who present with a better prognosis of consciousness shown a significant FC increase in the partial DMN [28]. Furthermore, these findings emphasize the importance of cross-hemispheric FC in posterior DMN nodes associated with the level of consciousness in patients with sTBI [10]. Although firm conclusions cannot be reached at present study, we could anticipate that the integration and reconstruction of the DMN network contributes to the recovery of consciousness after sTBI [29].

7.1. Limitation

An important limitation of this study is ROI does not define VTA boundary exactly. A 3-mm sphere of ROI could inevitably blur the boundary of VTA, such as anterior at the CSF, posterior at the coronal section, superior at the top of the superior colliculus, inferior at the bottom of the red nucleus, and lateral in the sagittal slice. The present findings are further limited by small sample size. In addition, the diffuse axonal or multi-focal injury could preclude definitive conclusions about the subcortical-cortical interplay in coma.

Ethical Approval/Informed Consent This study was approved by the Medical Ethics Committee of Shanghai Ninth people’s hospital. All procedures performed were in accordance with the ethical standards of the institutional committee.

Production notes

Author contribution statement

Canxin Xu & RuiZhe Zheng: Conceived and designed the experiments; Performed the experiments; Wrote the paper.
LaiYang Zhou: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.
DongFu Feng: Conceived and designed the experiments.

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Data availability statement

The data that has been used is confidential.

Declaration of interest’s statement

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.heliyon.2023.e15279>.

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