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A synergistic approach for identifying disrupted functional brain subnetworks in patients with chronic disorders of consciousness due to anoxic brain damage

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Abstract Determining the form of chronic disorder of consciousness is a challenging task in clinical practice, highlighting the need for objective diagnostic methods to assess the depth of impairment of consciousness. This study contributes to the development of more effective diagnostic and prognostic algorithms and biomarkers for patient management. Resting-state functional MRI data from 15 patients and 12 healthy controls were acquired using a 1.5 T system and processed using the statistical parametric mapping package. A connectivity matrix was constructed to assess brain connectivity, and statistical analyses including permutation tests, network-based statistics, and geodesic distance were used to identify significant differences in network measures between controls and patients. Our results revealed significant differences between the functional networks of the patient and control groups at both local and global levels, with altered metrics of node strength, clustering, and global efficiency. Notably, subcortical structures such as the thalamus, caudate nucleus, and raphe dorsalis nucleus showed disruptions in patients, consistent with the role of these regions in the basal ganglia-thalamo-cortical circuit. Our findings provide insight into the complex problem of how information is processed in the functional brain network in chronic disorders of consciousness, beyond the mere localization of functions.

1 Introduction

In clinical practice, establishing the form of chronic disorder of consciousness (DoC) is a challenging task due to the minimal or inconsistent ability to contact the patient. For the last 30 years, the over-diagnosis of unresponsive wakefulness (UWS) and vegetative state (VS) has been reaching 40% [1–4], meaning that almost half of patients diagnosed with VS who do not exhibit behavioral reactions have a certain level of hidden consciousness [5–10].

From a prognostic perspective, behavioral assessments, if performed repeatedly and thoroughly, are an important part of forming a clinical judgment. For instance, the Glasgow Outcome Scale and Coma Recovery Scale-Revised (CRS-R) demonstrate higher prognostic efficiency in comparison with other clinical variables [11]. However, such methods, being subjective, are highly dependent from the examiner's experience and the strict adherence to the examination protocol [12, 13]. Besides, there is a factor of a coincidence of diagnostic criteria in the differential diagnosis of chronic DoC: distinguishing between reflex and directed reactions of the patient is a non-trivial task and requires significant qualifications and experience of the neurologist [14, 15]. The clinical assessment of the

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level of consciousness is also influenced by the level of wakefulness and attention, the state of the motor and sensory spheres, the functions of perception and speech, the presence of pain syndrome, as well as the patient's immobilization [16, 17].

The application of objective instrumental diagnostic methods in the everyday practice of neuro reanimation unit holds significant potential for assessing the depth of consciousness impairment [6]. Given the current understanding of the structural–functional basis of consciousness as the highest mental function of the brain, neuroimaging methods, such as high-resolution functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI) of the brain's white matter, and other brain activity research techniques, are considered among the most promising for developing more effective diagnostic and prognostic algorithms for managing patients with chronic consciousness disorders. Until recently, fMRI research in the context of this clinical issue primarily focused on analyzing specific brain activation patterns in response to commands or during passive perception of stimuli [18]. Several studies have demonstrated that patients diagnosed with UWS may show cortical activity similar to that of healthy individuals, associated with speech perception and interpretation, processing of visual stimuli, as well as imagination and other cognitive processes [19–22].

Despite its clear advantages, fMRI with tasks has certain methodological limitations and requires significant time and labor. As a result, recent years have seen a shift in research focus toward the use of resting-state fMRI, which registers spontaneous brain activity in the absence of tasks or external stimulation [23–29]. This method has several key advantages. First, it does not require tasks or stimuli, eliminating the influence of individual cognitive strategies on brain activity and simplifying the preparation for the study. Second, resting-state fMRI takes significantly less time (around 10 min) compared to task-based fMRI. Third, this method of registration allows for standardization of the research protocol. Furthermore, an approach that aims for a more holistic assessment of brain activity opens up new opportunities for studying chronic DoC from the perspective of connectomics [30]. In this study, we investigated the damage to functional connectivity of the brain (according to rsfMRI) in a group of patients with chronic DoC resulting from a homogeneous etiology—anoxic brain injury.

Although behavioral assessments are an important part of forming a clinical judgment, these methods, being subjective, may be considered unreliable without additional diagnostic procedures [15]. The extension of standard protocols with instrumental methods to study brain activity can significantly improve the accuracy of prognosis in patients with chronic DoC [31, 32].

In the present paper, we propose a method to detect specific network-based biomarkers via multi-level analysis of fMRI data. Functional connectivity (FC) restored from fMRI data reveals the topology of the whole-brain network and allows to study the connectivity features in normal and pathological states of the cortex [33]. An extensive research in this area revealed normal and abnormal FC patterns corresponding to the various brain states. These biomarkers can be used to evaluate brain connectivity alterations in schizophrenia [34–36], early mild cognitive impairment [37, 38], Alzheimer's disease [39–42], autism spectrum disorder [43–46], and various mental disorders [34, 47–50]. Brain functional connectivity analysis allows to level out the individual variability of fMRI and identify stable patterns of interactions between brain areas that are most informative for detecting different levels of chronic DoC [23]. Chronic DoC patients demonstrate the disrupted FC patterns in thalamus, pallidum, and cortical networks [51, 52]. The study [53] provided evidence that addition of fMRI-based resting-state FC to the clinical variables can significantly increase diagnostic accuracy of patients with chronic DoC. Generally, there is a consensus that FC biomarkers can benefit the medical workers by increasing the reliability of the diagnosis.

In the present study, we consider the various quantifications of resting-state fMRI FC of the patients diagnosed with vegetative state and minimally conscious state. We perform a statistical analysis of the network measures to reveal the differences between these two groups of patients and healthy control group. We show that the approach based on graph-theoretical analysis allows a more accurate assessment of the state of consciousness and reveals network disruptions corresponding to the chronic DoC.

2 Materials and methods

2.1 Subjects

The study included 15 patients (8 men, 7 women) with chronic consciousness impairments (vegetative state or minimally conscious state) due to anoxic brain injury (DoC group). All patients were admitted to the Federal Research and Clinical Center for Intensive Care Medicine and Rehabilitology (Moscow, Russia) between 2022 and 2024. The average age of the patients was 39 (IQR 32–47) years. Detailed patient data, including etiology, duration of ischemia, glucose tolerance, and scores on the consciousness depth assessment scales, are provided in Table 1.

The healthy control (HC) group consisted of 12 individuals (6 men, 6 women) with an age of 41.5 (IQR 33.5–45.0) years. Healthy volunteers, as well as family members of the patients, signed informed consent to participate in the study. The study was carried out in accordance with the biomedical ethical principles outlined in the 1964 Helsinki

Table 1 Demographic and clinical data of the patients included in the present study

Patient ID	Sex	Age	Diagnosis	Etiology	CRS-R	FOUR	Ischemia duration	Glucose tolerance
1	F	39	MCS−	Postoperative	9	13	Acute	No
2	M	64	MCS+	Post Covid-19	11	13	Chronic	Yes
3	M	40	MCS−	Post Covid-20	7	9	Chronic	Yes
4	F	49	UWS	Postoperative	5	6	Acute	Yes
5	F	40	UWS	Postoperative	6	9	Acute	No
6	M	32	UWS	Postoperative	4	7	Acute	No
7	F	62	UWS	Post Covid-19	3	12	Chronic	Yes
8	F	44	UWS	Medications (a/b)	1	3	Acute	No
9	M	47	MCS−	Postoperative	11	13	Acute	No
10	F	30	UWS	Postoperative	5	6	Acute	No
11	M	51	UWS	Postoperative	3	9	Acute	no
12	M	32	UWS	Cardiac arrest	5	13	Acute	Yes
13	M	39	UWS	Alcohol abuse, cardiac arrest	5	11	Chronic	Yes
14	M	37	MCS−	Drug use	8	14	Chronic	No
15	F	39	MCS+	Anaphylaxis	12	13	Acute	No

CRS-R Coma Recovery Scale-Revised, *FOUR* full outline of unresponsiveness, *MCS* minimal conscious state, *UWS* unresponsive wakefulness syndrome, *a/b* antibiotics

Declaration and its subsequent revisions, and received approval from the local Bioethical Committee of the Federal Research and Clinical Center for Intensive Care Medicine and Rehabilitology (Moscow, Russia). All participants provided voluntary written informed consent, authorizing the publication of any potentially identifiable images or data included in this article.

Clinical assessment of consciousness was performed using the FOUR (full outline of unresponsiveness) Score [54], Glasgow Coma Scale [55, 56] and CRS-R [57]. The lowest item on each subscale represents reflexive activity, while the highest item represents cognitively mediated behaviors by addressing to auditory, visual, motor, oromotor, communication, and arousal functions.

2.2 Data acquisition

Resting-state functional and anatomical images were acquired using a 1.5 T Siemens Essenza (Siemens, Ltd., Germany) with an eight-channel head coil. Each resting-state functional run consisted of 300 T2-weighted echoplanar images (EPIs). The imaging parameters were as follows: 3.9 $\times$ 3.9 mm mm in-plane voxel size, covering the whole-brain volume 4.0-mm slices, interslice gap 0.8 mm, repetition time (TR) = 3670 ms, echo time (TE) = 70 ms, 64 $\times$ 64 matrix. In addition to the functional images, we collected a high-resolution T1-weighted anatomical scan for each participant (192 slices, resolution 1 $\times$ 1 $\times$ 1 mm, TR = 10 s, TE = 4.76 ms, 256 $\times$ 256 acquisition matrix).

2.3 Preprocessing

The data obtained in the study were processed using the SPM statistical processing package [58], executed on the MATLAB platform (version 2019b). Standard procedures were followed for preprocessing, which included motion correction, co-registration with high-resolution T1, and normalization to the Montreal Neurological Institute (MNI) standard space.

We divided the brain volume into 165 distinct regions using the anatomical atlas AAL3 [59]. This atlas was selected due to its widespread adoption in functional network analysis. To evaluate the connectivity between pairs of brain regions, we constructed a connectivity matrix. This process involved calculating the mean BOLD (blood oxygen level dependent) time series for each of the 165 brain parcellations that served as nodes in our analysis. After detrending these time series, we computed Pearson correlation coefficients for all possible pairs of averaged parcellation activities. The resulting connectivity matrix represents the functional brain network, illustrating the relationships between different brain regions based on their correlated activity patterns.

2.4 Network metrics

Our analysis focused on the topology and macroscale properties of functional networks by considering three key network metrics: node strength (NS), eigenvector centrality (EC), and clustering coefficient (CC). We computed and compared the distributions of these metrics across nodes (local level) and network-wide averages(global level) to gain insight into connectivity patterns, specifically looking at segregation and integration characteristics within brain networks:

- Node strength (NS) quantifies the influence of a node within a network based on its direct connections to other nodes, by summing the absolute edge weights associated with its connections. Normalization is applied to ensure comparison, with higher values indicating higher centrality within the network [60].
- Eigenvector centrality (EC) measures self-referential importance. Nodes receive increased importance based on their connection to other important nodes. The eigenvector centrality of one node i is equivalent to the ith element of the eigenvector corresponding to the largest eigenvalue of the adjacency matrix [61].
- Clustering coefficient (CC) assesses the level of connectivity between neighboring nodes. The weighted clustering coefficient determines the average connectivity intensity within triangle structures associated with each node, accounting for the strength of the relationships [62].

Statistical test (Mann–Whitney U test) was used to identify any significant differences in global network measures between the control group and patients for each metric. Statistical differences between network characteristics at the local level were calculated from the difference of group averages, with a permutation test between groups (50,000 permutations) to identify significantly changed nodes at the $p = 0.05$ level with Bonferroni correction of multiple comparisons [47].

The network-based statistic (NBS) approach [63] was employed to identify statistically different subnetworks between the groups at the $p = 0.05$ level with 50,000 permutations applied and the t-test with threshold value 3.5.

2.5 Geodesic distance

The geodesic distance measure is a valuable tool for quantifying the dissimilarity between correlation matrices, which represent functional connectivity patterns [64]. Its use in fMRI allows researchers to compare and analyze brain networks across different conditions, subjects, and time points, providing insights into the organization and dynamics of brain function. For two symmetric matrices $\mathbf{A}$ and $\mathbf{B}$, the geodesic distance $d(\mathbf{A}, \mathbf{B})$ can be computed using the following formula:

$$d(\mathbf{A}, \mathbf{B}) = \left|\log(\mathbf{A}^{-1/2}\mathbf{B}\mathbf{A}^{-1/2})\right|_F, \tag{1}$$

Here, log denotes the matrix logarithm, and $|\cdot|_F$ is the Frobenius norm. $\mathbf{A}^{-1/2}$ is the inverse square root of matrix $\mathbf{A}$, as that this definition assumes that the matrix $\mathbf{A}$ is invertible.

Advantages of such approach include:

- Invariance to linear transformations. The geodesic distance is invariant to linear transformations, which makes it a robust measure for comparing correlation matrices.
- Geometric interpretation. It provides a geometric interpretation of the dissimilarity between matrices, which is more intuitive and meaningful in the context of Riemannian geometry.
- Sensitivity to small changes. The geodesic distance is sensitive to small changes in the structure of the matrices, making it a powerful tool for detecting subtle differences in functional connectivity.

In our study, we measure the geodesic distance for the functional connectivity matrices of all subjects relative to the mean correlation matrix of the control group, which we take as the norm.

Table 2 Results of statistical comparison using Mann–Whitney U test of global network metrics between HC and DoC groups

Global metric	U, HC > DoC	p value
Eigenvector centrality	− 1.7810	0.0749
Node strength*	− 2.6593	0.0078
Clustering coefficient*	− 2.6105	0.0090
Global efficiency*	− 2.4641	0.0137

*Denotes the metrics demonstrating significant difference

3 Results

3.1 Network metrics

3.1.1 Global level

The statistical test of global network characteristics allowed us to identify important trends, in particular that there are some significant differences between groups for most network measures shown in Table 2.

In summary, the statistical tests suggest that while there is no significant difference in eigenvector centrality between the control and patient groups, there are significant differences in node strength, clustering coefficient, and global efficiency. Specifically, the patient group shows higher values for these measures compared to the control group, as reflected by the negative test statistics. Node strength shows the largest effect. These results may indicate that network properties are altered in the patient group in a way that affects node strength, clustering, and global efficiency.

3.1.2 Local level

Figure 1 illustrates the distributions across nodes of the differences between the group-averaged network eigenvector centrality, node strength, and clustering coefficient for the HC and DoC groups. As one can see in Fig. 1, there are a number of nodes with significant differences between groups according to the network metrics. Only the Caudate R is significant for the EC metric (see Fig. 1a, green patch), for the CC metric, there are 14 significant nodes (see Fig. 1b), and for the NS metric—16 nodes (see Fig. 1c), most of which are the same, except for the Thal Re R and SN pr L (see Table 3 for details). The direction of the effects is similar to the global metrics: the group of patients demonstrates higher values.

Figure 2 demonstrates the results of NBS application to reveal significantly different connections between the HC and DoC groups.

According to the NBS results (see "blue" connections in Fig. 2), the functional network of the control group has 38 significantly stronger connections compared to the DoC group, connecting mainly frontal regions [mainly rectus gyrus (14/38) and orbitofrontal cortex (OFC, 21/38)], temporal regions (16/38, mainly temporal pole and inferior temporal gyrus) and subcortical structures [nucleus accumbens (14/38), thalamus and cerebellum]. These connections form the character triangle between the nucleus accumbens, the temporal pole and the orbitofrontal cortex. The OFC (both medial and lateral divisions) shows strong connectivity with the rectus gyrus, both left and right, and the temporal pole (middle and inferior) shows connectivity with the putamen, rectus gyrus, and OFC.

The direction DoC > HC gives 74 significantly different connections (see "red" connections in Fig. 2). These results suggest that the DoC group exhibits unique functional connectivity patterns, particularly involving the thalamus (25/74), olfactory system, frontal lobe, cingulate gyrus, and cerebellum. These connections may reflect compensatory mechanisms or underlying neurological differences in the DoC group.

3.2 Geodesic distance

The statistical test shows a significant difference in the geodesic distance between the DoC and HC groups: $U = 4.5244$, $p < 0.001$, the distributions of which are shown in Fig. 3A. The significant results of the Mann–Whitney test, together with the visual evidence from the figure, strongly suggest that the geodesic distance in the DoC group is significantly higher than in the HC group.

In addition, geodesic distance values were negatively correlated with the FOUR scale ($r = -0.58$, $p = 0.02$, see Fig. 3B), suggesting that geodetic distance may reflect disease severity as a diagnostic or prognostic indicator. In contrast, the correlation with the CRS-R scale was insignificant ($r = -0.40$, $p = 0.13$, see Fig. 3C).

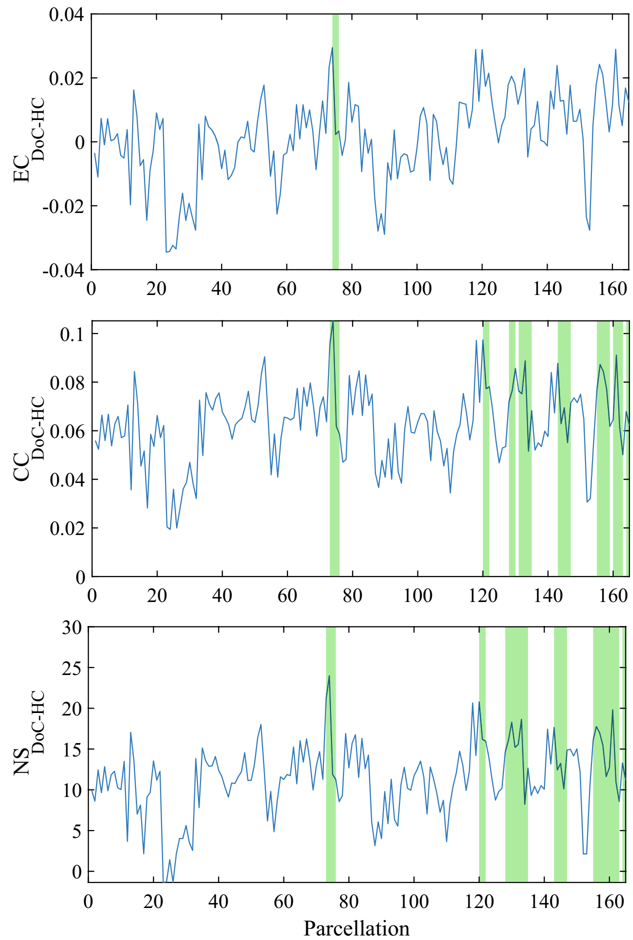

Fig. 1 The distributions across nodes of the differences between the group-averaged network metrics (EC, CC, NS) for the HC and DoC groups. Green patches indicate nodes with significant differences. These were identified by the permutation test

Table 3 Nodes with significant differences between groups (DoC>HC) for CC and NS metrics

Node	CC metric	NS metric
Caudate L/R	+	+
Thal LP R	+	+
Thal IL R	+	+
Thal Re R		+
Thal MDm R	+	+
Thal MDl R	+	+
Thal PuA R	+	+
Thal PuL R	+	+
VTA R	+	+
SN pc L/R	+	+
SN pr L		+
Red N L/R	+	+
Raphe D	+	+

"+" Denotes nodes significant for CC and NS metrics, respectively

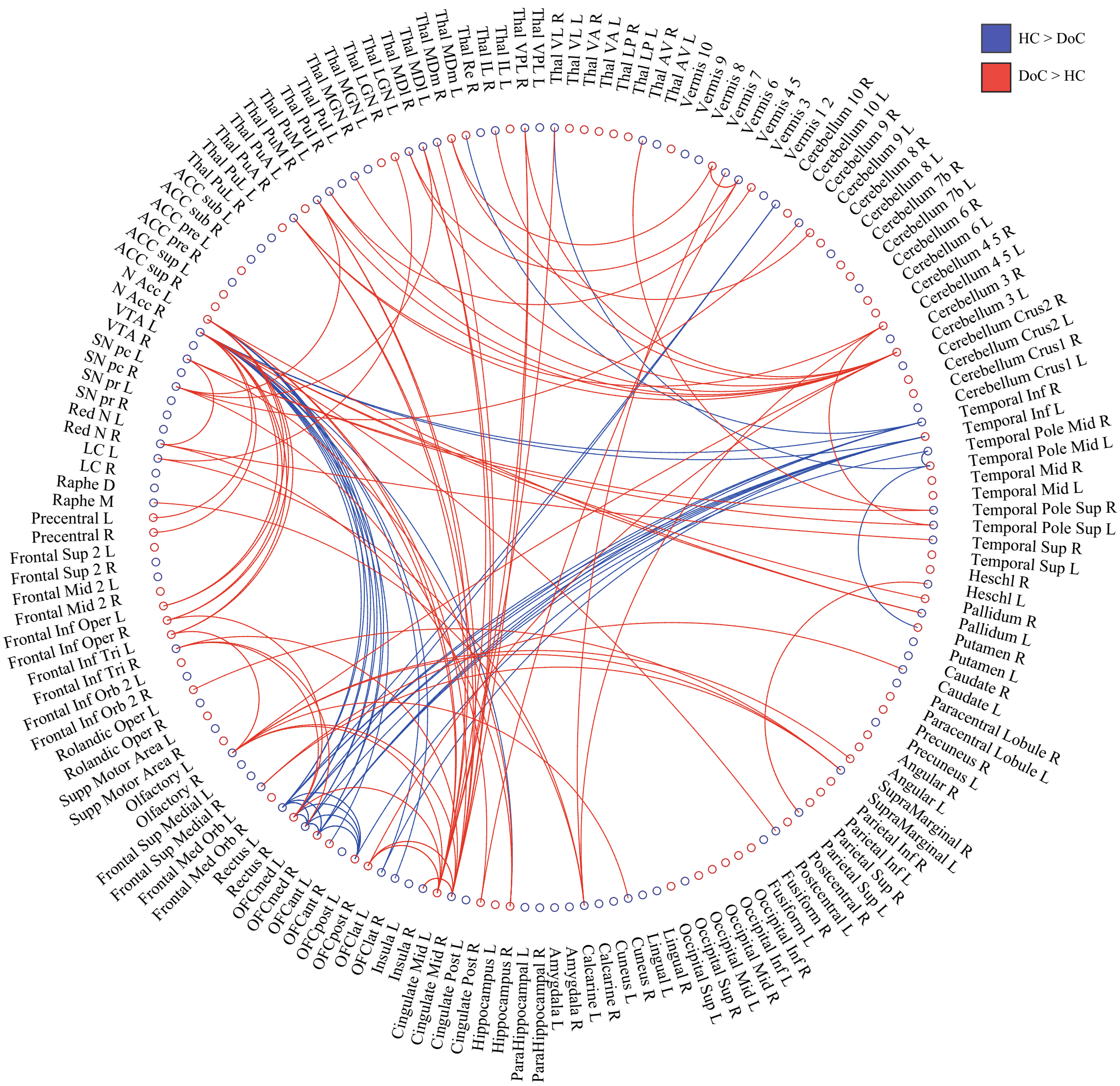

Fig. 2 Significantly different connections between the HC and DoC groups revealed by the NBS method; blue connections correspond to the direction HC>DoC, red—DoC>HC

4 Discussion

4.1 Network measures

4.1.1 Global level

At the global level, differences between patients and controls were evident in such network metrics as node strength, clustering, and global efficiency. This result is consistent with the trend of research that has shifted attention from the limited "where" question to the more complex "how" question, emphasizing the relationship between information and its implementation rather than just the localization of functions. Building on the idea that to understand consciousness, complex network interactions are best analyzed in a spatiotemporal context [65], researchers have argued that changes in network connectivity over time reflect fluctuations in underlying brain states such as wakefulness or consciousness [66]. Previous research suggests that temporal changes in the distribution of network patterns can be used to distinguish between different states of consciousness, including sleep, anesthesia, and patients with severe brain damage. This has been confirmed by numerous experiments, including those using large samples [66–69] and others.

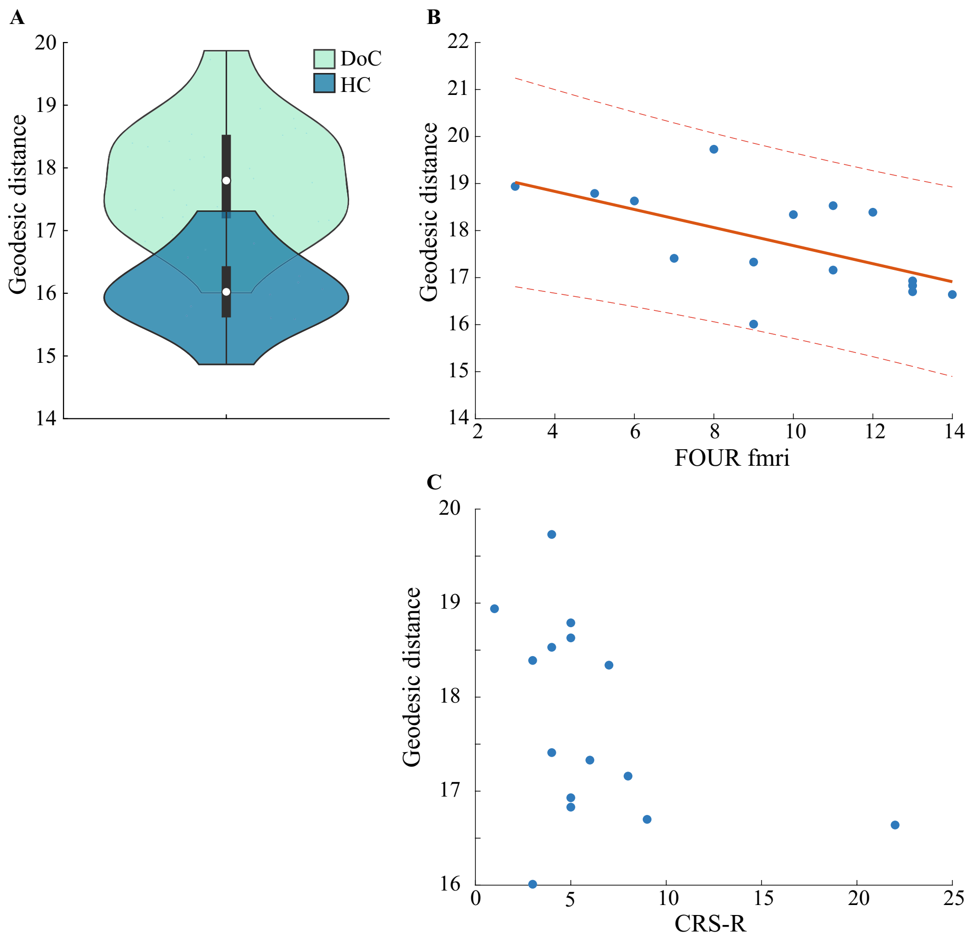

Fig. 3 **A** Distributions of geodesic distances for the HC and DoC groups; mean is depicted by circles, quartile range—by squares and outlines. **B** Correlation of geodesic distance of individuals with FOUR score. Linear approximation with confidence intervals at 95% is shown in red

4.1.2 Local level

At the local level in patients, changes in metrics relative to healthy subjects were obtained in subcortical structures: the caudate nucleus area on the right and left, in the thalamic nuclei, red nucleus, right ventral tegmental area (VTA) and nucleus raphe dorsalis. Our result confirms the role of the thalamus and caudate nucleus as part of the basal ganglia-thalamo-cortical circuit, which plays an important role in maintaining the critical balance between excitation and inhibition required for cortical activation, movement control, and high-level cognition [70–74]. VTA, as has been shown, modulates human consciousness via connectivity with the cortical default mode network (DMN) [75]. The role of DMN in maintaining level of consciousness has been shown experimentally [24, 76, 77]. Moreover, there is some evidence that dopaminergic modulation realized through the VTA may be a central mechanism for maintaining consciousness [75].

The altered function of the nucleus raphe dorsalis possibly reflects such a clinical manifestation, common among DoC patients, as disruption of the sleep–wake cycle. It has been hypothesized that the nucleus raphe dorsalis plays an important role in the regulation of the sleep–wake cycle [78]. Optogenetic activation of 5-HTergic neurons in the nucleus raphe dorsalis has been shown to induce active wakefulness in mice [79]. In addition, these neurons, directed to the ventrolateral hypothalamus, promote arousal by de-inhibition of orexinergic neurons [80].

4.2 Geodesic distance

We obtained a negative correlation between the geodesic distance parameter and the FOUR scale. The FOUR scale is a method for assessing the depth of central nervous system depression in the intensive care unit. This scale is not sensitive for differentiating between chronic disorders of consciousness: the minimally conscious state and the vegetative state because it only assesses eye response, motor response, brainstem reflexes, and respiratory pattern. Nevertheless, this scale can be used in DoC patients to assess the depth of impairment of consciousness, with the lower the score obtained in the examination, the more severe the patient's condition. Moreover, FOUR is the only scale to date with good predictive ability for recovery after 30 days [81]. In our case, the negative correlation of

FOUR scale scores with geodesic distance measures reflects a situation where severity of brain damage reduces the similarity of patients' functional connectome to normality. Interestingly, in doing so, we did not obtain a similar result for the CRS-R. Although this scale allows a more comprehensive assessment of brain functioning ranging from sensory functions and wakefulness to goal-directed activity [57]. Other authors have been able to identify patterns of brain activity in DoC patients that correlate with CRS-R scores [82], although this study used a measure of local BOLD intensity rather than an integrative measure of connectome normality.

4.3 Limitations

In our and other similar comparative studies, changes in states of consciousness are closely related to changes in levels of behavioral activity and cognitive abilities, as well as to other processes associated with transient states. Regardless of the metric chosen to measure brain activity, this relationship makes it difficult to unambiguously establish a link between brain function and consciousness, which limits the ability to clearly interpret the findings. Although these metrics are often interpreted as reflecting changes in the state of consciousness, it has yet to be demonstrated that they are not merely indicators of changes in behavioral reactivity.

Another limitation of our study is the relatively small group of patients and, respectively, controls. This does not allow us to generalize our results, but allows us to consider that our approach based on topological measures of fMRI-based functional brain networks may be promising for analyzing patients diagnosed with DoC.

5 Conclusion

Our findings provide insights into the differences in functional brain network organization between patients and controls at both local and global levels. The findings suggest that changes in network connectivity may be associated with altered consciousness in patients. The results support the notion that complex network interactions are crucial in understanding consciousness, and changes in network patterns over time may reflect fluctuations in underlying brain states such as wakefulness or consciousness.

Changes in subcortical structures, including the thalamus, caudate nucleus, VTA, and nucleus raphe dorsalis, were observed in patients, suggesting their role in maintaining consciousness. The results confirm the importance of the basal ganglia-thalamo-cortical circuit in maintaining the balance between excitation and inhibition required for cortical activation, movement control, and high-level cognition. The VTA's connectivity with the cortical default mode network (DMN) may play a central role in modulating human consciousness, and dopaminergic modulation through the VTA may be a key mechanism for maintaining consciousness.

Our findings have implications for the understanding of consciousness and the development of diagnostic and therapeutic strategies for patients with DoC. Further research is needed to investigate the causal relationships between changes in network connectivity and consciousness, and to explore the potential of network-based biomarkers for diagnosing and monitoring DoC.

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Data and code availability statement The data presented in this study are available on request from Larisa Mayorova.

Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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