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Patient-specific factors are associated with distinct brain network connectivity in disorders of consciousness

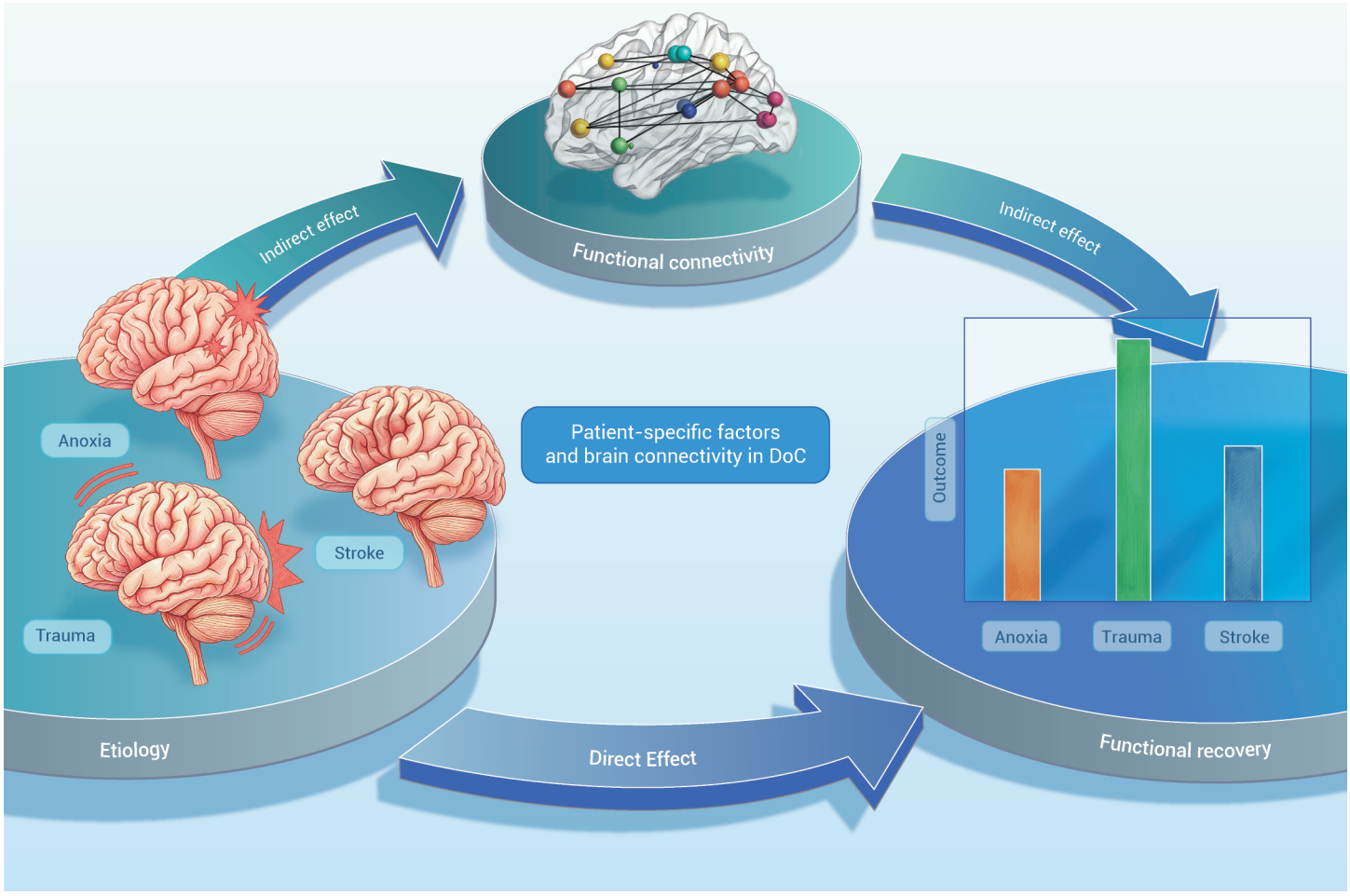
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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Clinical characteristics are associated with distinct large-scale brain network connectivity.
- Etiology related connectivity are closely linked to patients' consciousness level and functional recovery.
- Internetwork connectivity accounted for greater functional recovery in traumatic brain injury patients.

REPORT Neuroscience

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Patient-specific factors are associated with distinct brain network connectivity in disorders of consciousness

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Disorders of consciousness (DoC) arise from diverse etiologies and exhibit substantial clinical heterogeneity, including variations in patient age and time since injury. However, how these clinical characteristics relate to large-scale brain network connectivity and are associated with consciousness levels and functional outcomes remains poorly understood. In this study, resting-state functional magnetic resonance imaging (rs-fMRI) data from 128 DoC patients were analyzed. Functional connectivity (FC) patterns linked to key clinical characteristics were identified using an explainable machine learning framework. Statistical path analysis was then employed to assess whether intra- and inter-network FC account for the statistical effects of clinical characteristics on consciousness level and functional recovery. Patients with traumatic brain injury (TBI) and younger age exhibited higher consciousness levels and greater recovery potential, whereas time since injury showed no such relationship. Each clinical characteristic corresponded to distinct, largely non-overlapping FC patterns distributed across different large-scale brain networks. Notably, etiology-related intra- and inter-network connectivity reliably indexed patients' recovery outcomes. Statistical path analysis further demonstrated that inter-network FC could statistically account for the superior recovery observed in TBI compared to anoxic patients. Clinical characteristics are associated with large-scale brain network connectivity in DoC, and are linked to the potential of functional recovery through these connectivity patterns. These findings highlight the value of integrating clinical-contextualized connectivity biomarkers into individualized prognostic assessment and therapeutic strategies.

INTRODUCTION

Disorders of consciousness (DoC), including the vegetative state/unresponsive wakefulness syndrome (VS/UWS) and minimally conscious state (MCS), are among the most severe consequences following acquired brain injury. These conditions are marked by profound impairments in awareness and responsiveness, posing substantial challenges for accurate diagnosis, prognostication, and treatment. Despite the widespread use of standardized behavioral assessments, such as the Coma Recovery Scale-Revised (CRS-R),[1] considerable inter-individual variability persists in both the level of residual consciousness and the potential for recovery. A deeper understanding the neurobiological and clinical characteristics contributing to this variability is essential for improving prognostic accuracy and guiding personalized treatment strategies.

Among clinical characteristics, etiology, age, and time since injury have been repeatedly implicated in relating to both consciousness presentation and recovery outcomes in patients with DoC.[2-8] DoC are caused by various etiologies, including anoxia, traumatic brain injury (TBI), and stroke.[9,10] Prior studies have shown that diagnostic accuracy varies by etiology, with anoxic injuries yielding the highest diagnostic sensitivity, followed by traumatic and vascular causes.[11] Differential distributions of VS/UWS and MCS across etiological subtypes were also observed.[12] Among etiologies, TBI is generally associated with better recovery and lower mortality compared to anoxic or vascular injuries, across both adults and pediatric populations.[2,7,13,14] Even within TBI subgroups, outcomes vary by mechanism of injury, patients with sports-related TBI tend to recover better than those with non-sports-related causes, after controlling for confounders.[15] Younger age and shorter time since injury are additional factors associated with a higher likelihood of regaining consciousness and achieving more favorable functional outcomes.[16,17] Prognostic models that integrate etiology, patient age and time since injury would achieve optimal predictive performance.[18,19] Taken together, these findings underscore the need to systematically incorporate clinical variables into the design of personalized medical and rehabilitative strategies.[20]

The rs-fMRI has emerged as a powerful tool for probing large-scale brain network organization,[14] with potential applications in detecting residual consciousness and predicting recovery outcomes in DoC patients. Early work established that the default mode network (DMN) connectivity is reduced in DoC patients and correlates with the severity of consciousness impairment.[21] Subsequent studies extended these findings by demonstrating that FC disruptions are not limited to the DMN but also involve the executive control network (ECN) and auditory network (AN).[22] Building on this, further research revealed that FC within multiple large-scale networks, including the DMN, salience network (SN), sensorimotor network (SMN), AN, and visual network (VN), correlates with CRS-R scores and can discriminate between MCS and VS/UWS patients.[23-27] Importantly, these network-level alterations also carry prognostic value. DMN connectivity[24] and FC between the posterior cingulate cortex and medial prefrontal cortex (PCC-mPFC)[26] differentiate recovered from non-recovered patients. Convergent evidence further supports the association between FC and functional outcome,[25] and subsequent work has demonstrated that FC-based models can predict functional recovery with considerable accuracy.[19] More recently, the field has expanded beyond static FC to examine dynamic connectivity metrics, which capture temporal fluctuations in network interactions and may offer additional insights into the neural correlates of consciousness.[28]

Few studies have investigated how clinical characteristics relate to differences in functional brain activity in DoC patients. Task-based fMRI has demonstrated preserved mental imagery responses in patients with TBI,[29,30] whereas such responses are often absent in those with nontraumatic brain injuries.[30] Recently, a rs-fMRI study has extended these observations by demonstrating etiology-dependent distinctions in brain function.[31]

Previous studies have primarily established associations between clinical characteristics and patients' consciousness levels and functional recovery, and has also linked brain connectivity to these clinical outcomes. However, it remains poorly understood how specific clinical characteristics are associated with FC alterations across brain networks in DoC, and how these connectivity changes account for the relationship between clinical characteristics and recovery outcomes.

To address these questions, we analyzed rs-fMRI data from a large cohort of patients with DoC, combined with detailed clinical assessments, and applied an analytical framework integrating predictive modeling with statistical path analysis. We sought to systematically evaluate (1) how clinical variables such as etiology, age, and time since injury are associated with alterations in FC across multiple large-scale brain networks, (2) whether these connectivity changes relate to consciousness level and functional outcome, and (3) to what extent FC accounts for the relationship between clinical characteristics and behavioral recovery. By linking clinical heterogeneity to distinct functional network signatures, this study aims to advance our understanding

of the associations underlying recovery variability in DoC and to inform the development of connectivity-based biomarkers for personalized prognostic assessment.

MATERIALS AND METHODS

DoC patients

This study included a total of 128 patients with disorders of consciousness (DoC) and 40 healthy control subjects across three datasets: '*Beijing 750*', '*Beijing HDxt*', and '*Guangzhou HDxt*'. Among these 128 patients, 112 were derived from the study by Song et al.,[19] and the remaining 16 were newly recruited for the present retrospective study. Inclusion criteria for patients required a diagnosis of DoC persisting for at least 28 days post-injury and the absence of severe structural brain damage or malformations. The *Beijing 750* dataset included 68 patients (49 VS/UWS and 19 MCS) and 30 healthy controls; *Beijing HDxt* included 36 patients (28 VS/UWS and 8 MCS) and 10 healthy controls; and *Guangzhou HDxt* included 24 patients (16 VS/UWS and 8 MCS). The *Beijing 750*and *Beijing HDxt* datasets were acquired at the PLA Army General Hospital in Beijing, using a GE Discovery MR750 3.0T scanner and a GE Signa HDxt 3.0T scanner, respectively. The *Guangzhou HDxt* dataset was collected at Guangzhou General Hospital of Guangzhou Military Command, using a GE Signa HDxt 3.0T scanner. Ethical approval was obtained from the Ethics Committee of the PLA Army General Hospital (protocol No: 2011-097 and 2011-0415) and the Ethics Committee of Guangzhou General Hospital of Guangzhou Military Command (protocol No: jz20091287). Informed consent was obtained from legal guardians of patients and from healthy control participants in accordance with institutional guidelines.

Diagnostic classification of MCS and VS/UWS was determined using the JFK Coma Recovery Scale–Revised scores.[1] Functional recovery outcomes were evaluated using the Glasgow Outcome Scale (GOS),[32] which was assessed at 29.8 ± 17.2 months post disease onset. All clinical assessments were performed by experienced neurosurgeons. Detailed demographic and clinical information is provided in Table 1. The healthy control group contained 18 females and 22 males, with their ages ranging from 21 to 60 (mean age: 37.78 ± 11.08 years). All clinical data utilized in this study, including MRI scans and clinical neurobehavioral assessments, were examined and collected as part of routine clinical care.

MRI acquisition

No sedatives or anesthetics were administered during MRI scanning. The rs-fMRI data were acquired using a T2*-weighted gradient echo sequence on either GE Discovery MR750 3.0T scanner or GE Signa HDxt 3.0T scanners. For the *Beijing 750* dataset, acquisition parameters were: TR/TE = 2000/30 ms; flip angle = 90°; 39 axial slices; thickness = 4 mm; FOV = 240 × 240 mm^2; matrix = 64 × 64, and 210 volumes. For the *Beijing HDxt* dataset, there were four sets of acquisition parameters: (1) TR/TE = 2000/30 ms; flip angle = 90°; 33 axial slices; thickness = 4 mm; FOV = 220 × 220 mm^2; matrix = 64 × 64; and 240 volumes; (2) TR/TE = 2000/30 ms; flip angle = 90°; 32 axial slices; thickness = 4 mm; FOV = 220 × 220 mm^2; matrix = 64 × 64; 210 volumes; (3) TR/TE = 2000/30 ms; flip angle = 90°; 32 axial slices; thickness = 4 mm; FOV = 192 × 192 mm^2; matrix = 64 × 64; 210 volumes; (4) TR/TE = 2000/30 ms; flip angle = 90°; 32 axial slices; thickness = 4 mm; FOV = 210 × 210 mm^2; matrix = 64 × 64; 210 volumes. For the *Guangzhou HDxt* dataset, acquisition parameters were: TR/TE = 2000/30 ms; flip angle = 90°; 35 axial slices; thickness = 4 mm; FOV = 240 × 240 mm^2; matrix = 64 × 64; and 240 volumes. The patients' rs-fMRI data were acquired at 5.7 ± 10.0 months post disease onset. No significant differences were found in age, time since injury, sex, diagnosis, or GOS score across the three scanners (Table S1). However, etiology distributions differed significantly (χ^2 = 12.70, P = 0.0129), driven by the absence of stroke patients in the Guangzhou HDxt dataset, which included only anoxia and trauma cases, whereas the Beijing 750 and Beijing HDxt datasets included all three etiologies (pairwise χ^2 tests, FDR-corrected P < 0.05). CRS-R score also differed across scanners (F(2,125) = 3.13, P = 0.0471), driven by lower scores in the Beijing HDxt dataset compared to Guangzhou HDxt (P = 0.0333, Tukey-Kramer corrected).

Table 1. Demographic and clinical characteristics of DoC patients.

Variable	Value
Age, years, mean (SD)	42.1 (14.4)
Time since injury, months, mean (SD)	5.7 (10.0)
Sex (%)	
Female	50 (39.1)
Male	78 (60.9)
Etiology (%)	
Anoxia	54 (42.2)
Trauma	42 (32.8)
Stroke	32 (25.0)
Diagnose (%)	
MCS	35 (27.3)
VS/UWS	93 (72.7)
CRS-R, mean (SD)	7.1 (3.1)
GOS, mean (SD)	2.4 (0.7)

Image preprocessing and functional connectivity analysis

The preprocessing steps for rs-fMRI data have been previously reported,[19] and the MATLAB codes are available at https://github.com/elifesciences-publications/pDOC. Data was preprocessed using SPM8. For all datasets, the first five volumes were discarded, and the remaining volumes were corrected for slice timing, realigned, and spatially smoothed using a 6 mm full-width at half maximum (FWHM) Gaussian kernel. Twelve head motion parameters (translations and rotations in three directions and their first derivatives), whole-brain signals, and linear trends were regressed out. Volumes with framewise displacement (FD) greater than1.5 mm were censored, and patients with fewer than 50 remaining volumes were excluded. The post-censoring FD values had no significant difference across three datasets or across etiology groups (Figure S1). Furthermore, no significant correlations with age and time since injury were observed (Figure S1). A band-pass filter (0.01–0.08 Hz) was applied to the retained volumes.

We focused on six previously implicated brain networks in DoC: default mode, executive control, salience, sensorimotor, auditory, and visual networks. Twenty-two regions of interest (ROIs) were defined within these networks following the same procedure as in the prior study.[19] The preprocessing pipeline[19] developed by Song et al. was designed to generate functional connectivity patterns in each patient's native imaging space. The ROI masks (https://github.com/elifesciences-publications/pDOC) were spatially transformed to each patient's functional space and resampled accordingly. To visually verify the registration, we presented example images of the warped ROIs for three DoC patients (Figures S2-S16). Additional registration details can be found in Song et al..[19] Functional connectivity between ROI pairs was computed as Pearson's correlation between the average time series across ROIs, resulting in 231 (22 × 21/2) pairwise FCs. Correlation coefficients were converted to Fisher's z-scores for further analysis.

SHAP analysis

To identify which brain networks were primarily associated with individual clinical characteristics, we applied Shapley Additive exPlanations (SHAP) analysis. We trained a support vector classification (SVC) model to classify etiology and support vector regression (SVR) models to predict age and time since injury using all 231 FCs as input features. Leave-one-out (LOO) cross-validation was employed for model validation, with nested feature selection was implemented within this framework. Specifically, in each outer LOO fold, we first performed ANCOVA (for the SVC model) or partial correlation (for the SVR models) on the training set, with scanner included as a covariate, to preselect FCs at an uncorrected threshold of p < 0.05. Subsequently, within the inner loop, a 5-fold stratified cross-validation was used to perform further

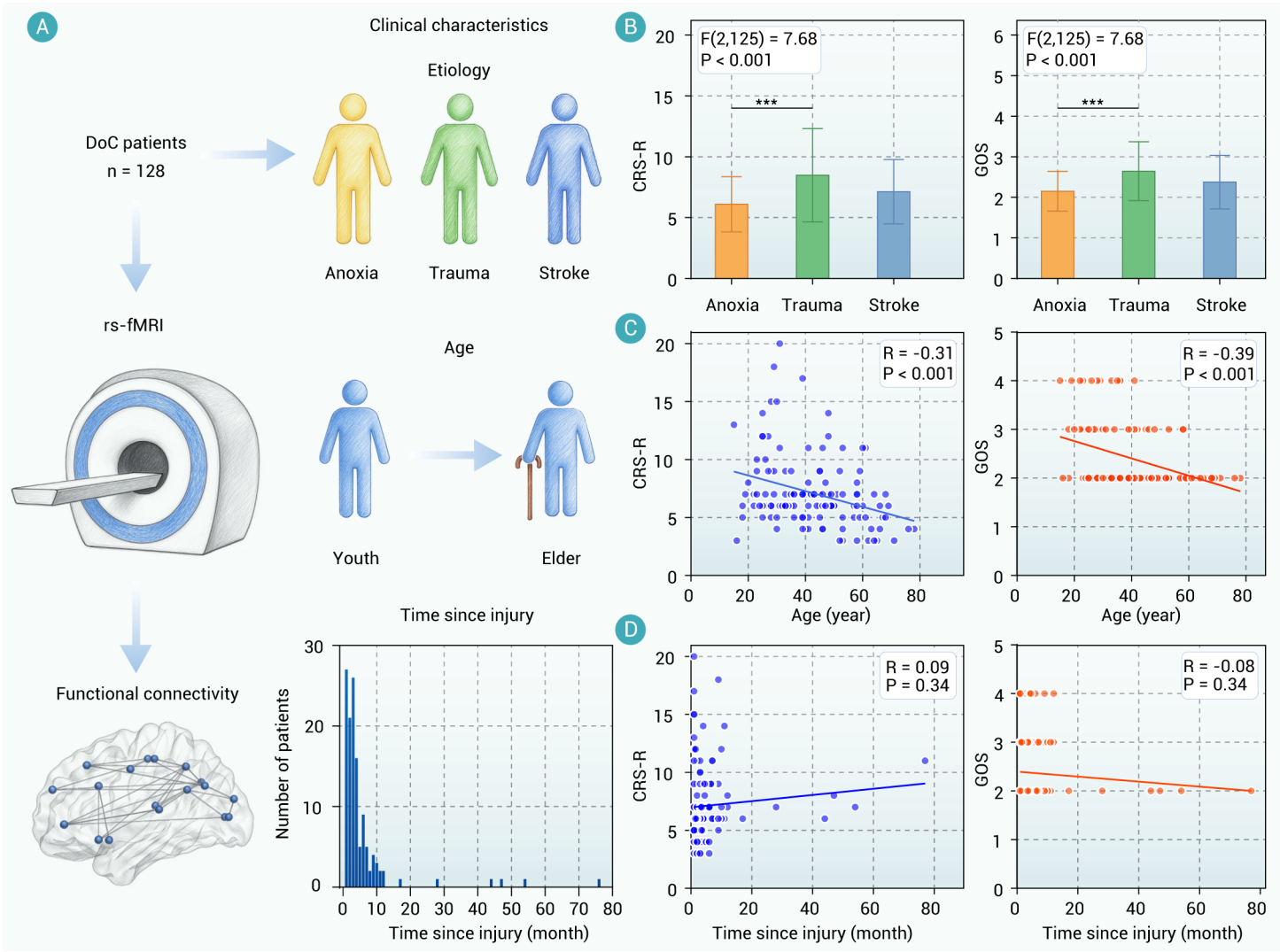


Figure 1. Associations between clinical characteristics, consciousness levels, and functional recovery in patients with disorders of consciousness (A) Overview of study design, integrating clinical, behavioral, and neuroimaging data. (B) Group comparisons of CRS-R and GOS scores across etiological subtypes (anoxia, traumatic brain injury, and stroke). Error bars denote standard error of the mean (SEM). *** P < 0.001, Tukey–Kramer corrected post hoc tests. (C) Scatterplots illustrating significant negative correlations between patient age and CRS-R (blue) and GOS (red) scores. (D) No significant associations were observed between time since injury and either CRS-R or GOS scores. Each data point represents an individual patient; solid lines depict linear regression fits.

feature selection on the preselected feature subset. To evaluate the reliability of feature selection, we calculated the selection frequency for each FC, defined as the proportion of the 128 LOO outer folds in which the FC survived the ANCOVA or partial correlation pre-selection. The SHAP[33] value was used to estimate the contribution of each FC feature to the model's prediction of their clinical characteristic. Absolute SHAP values were averaged across patients for each FC, and then averaged across all FCs within each brain network to derive the mean SHAP value per network. The brain network with the highest mean SHAP value was considered carried the most predictive information of the corresponding clinical characteristic. Analyses were conducted using the Python library of Scikit-learn.[34]

Statistical path analysis

Statistical path analyses were performed to test whether functional connectivity accounted for the statistical effects of clinical characteristics on consciousness level and functional recovery. Models were implemented using PROCESS macro[35] in SPSS version 26. The statistical mediation model decomposes the total association between an independent variable (X) and a dependent variable (Y) into: a direct effect (X→Y), and an indirect effect (X→M→Y), where the association between X and Y is statistically accounted for by a mediator variable (M).[36] Specifically, X is hypothesized to be associated with M, which in turn is associated with Y. This approach allows us to quantify the extent to which the clinical characteristics–outcome association is statistically explained by alterations in FC. For etiology (a multicategorical variable), we defined anoxic patients as the reference group (coded as 0 on both X_1 and X_2), while X_1 codes the trauma group and X_2 codes the stroke group. For each patient, intra- and inter-network FCs associated with etiology were averaged and used as the mediator variable M. Dependent variables were CRS-R scores (reflecting consciousness level) and GOS scores (reflecting long-term functional outcome). We tested four statistical mediation models to examine the indirect effect through functional connectivity: (1) *Etiology → Intra-network FC → CRS-R*, (2) *Etiology → Intra-network FC → GOS*, (3) *Etiology → Inter-network FC → CRS-R*, and (4) *Etiology → Inter-network FC → GOS*.

For age and time since injury (both continuous variables, X), their associated intra- and inter-network FCs served as the mediator variable (M), and CRS-R and GOS were the dependent outcomes (Y). Parameter estimates were obtained via ordinary least squares (OLS) regression, and 95% confidence intervals (CI) were generated via bootstrapping with 5000 repetitions.[36] Age, diagnosis, scanner and mean post-censoring FD were included as covariates in all statistical models with two exceptions: (1) diagnosis was excluded from models with CRS-R as the dependent variable due to strong collinearity; and (2) age was not included as a covariate when it served as the independent variable of interest.

Statistical analysis

Between-group comparisons of CRS-R scores, and GOS outcomes across

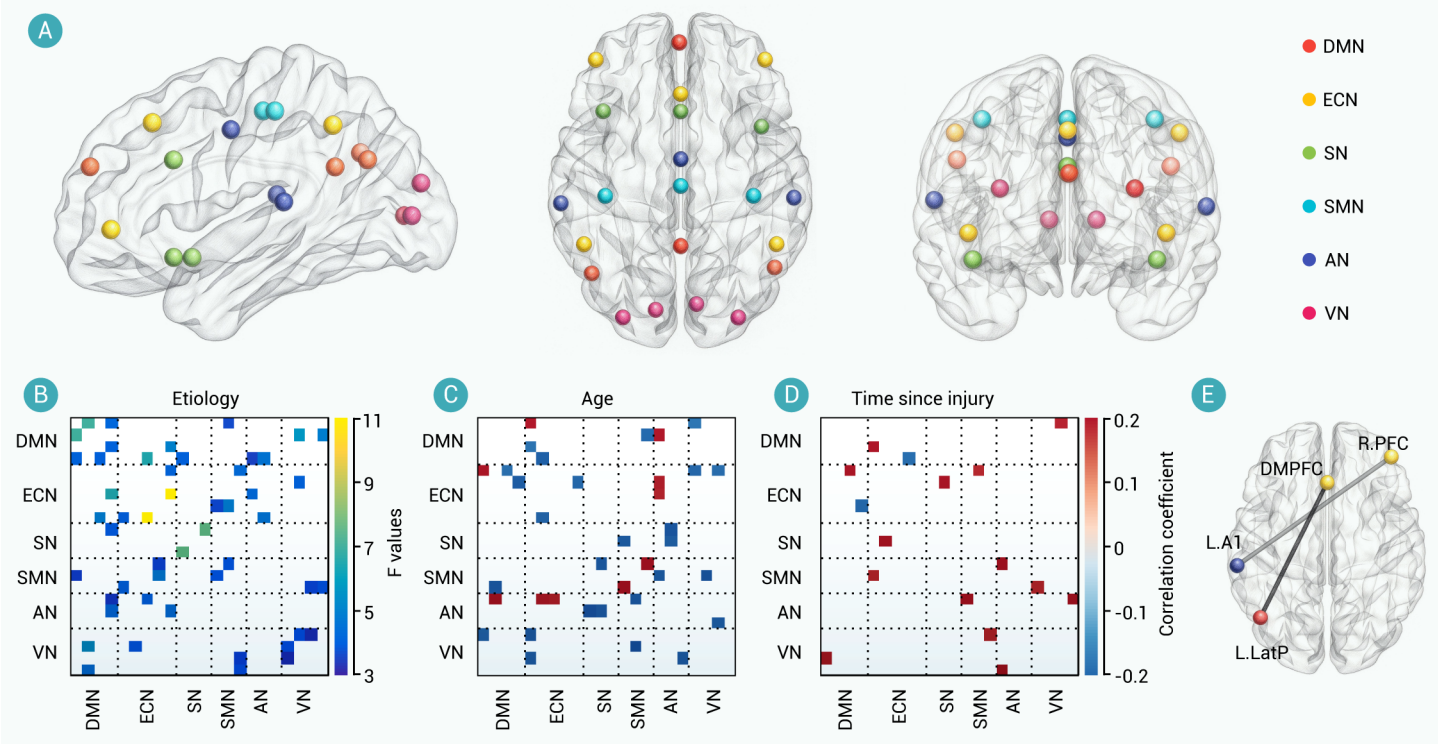


Figure 2. Associations between clinical characteristics and resting-state functional connectivity across large-scale brain networks (A) Schematic representation of the six cortical brain networks examined: default mode network (DMN), executive control network (ECN), salience network (SN), sensorimotor network (SMN), auditory network (AN), and visual network (VN). Each dot represents a network node (region of interest). (B) Functional connectivity matrices showing between-group differences among etiological subtypes (anoxia, traumatic brain injury, and stroke). Only FCs demonstrating significant differences (one-way ANOVA, $P < 0.05$; uncorrected) are shown. (C) FCs significantly associated with patient age, based on Pearson's correlation analysis ($P < 0.05$). (D) FCs significantly associated with time since injury, based on Pearson's correlation analysis ($P < 0.05$). (E) Common connectivity to etiology- and age-related FC (gray line), and shared connectivity between age- and time-associated FC (black line).

etiologies were conducted using one-way analysis of variance (ANOVA), followed by post-hoc pairwise comparisons with the Tukey-Kramer test. Correlations of CRS-R, and GOS scores with patients' age and time since injury were computed with Pearson's correlation. ANCOVA and partial correlation tests with scanner as covariate were used to identify etiology, age, time since injury related FCs. Comparisons of intra- and inter-network FCs between groups were assessed using the Mann-Whitney-Wilcoxon test (false discovery rate (FDR) corrected). Permutation tests (5,000 iterations) were performed to confirm the robustness of FCs identified by ANCOVA (etiology) and partial correlation (age and time since injury). For each iteration, the clinical characteristic of interest was randomly shuffled, and the corresponding statistic (F-value for ANCOVA, or partial correlation coefficient) was recomputed for each FC. The permutation P-value was calculated as the proportion of permuted statistics exceeding the observed statistic.

RESULTS

Clinical characteristics and their relationships with consciousness and recovery

A total of 128 patients with disorders of consciousness (DoC) were included in the study (Figure 1A & Table 1), comprising 54 patients with anoxic injury, 42 with traumatic brain injury (TBI), and 32 with stroke. Diagnostic classification into MCS or VS/UWS was determined using CRS-R scores. Functional recovery was assessed using the GOS score, with patients categorized into either the functional recovery group (FR; GOS ≥ 3) or the non-recovery group (FNR; GOS < 3).

To assess whether and how etiologies associate with consciousness and recovery, we have run group-level comparisons, which revealed that traumatic patients exhibited significantly higher levels of consciousness and better recovery outcomes than both the anoxic and stroke groups (Figure 1B). Mean CRS-R scores differed significantly across etiology groups ($F(2,125) = 7.68$, $P < 0.001$). Post-hoc comparisons using the Tukey-Kramer test revealed that the TBI group (8.5 ± 3.8, mean ± SD) had significantly higher CRS-R scores than the anoxic group (6.1 ± 2.3, $P < 0.001$), whereas the stroke group (7.1 ± 2.6) did not differ significantly from TBI ($P = 0.1255$) and anoxic ($P = 0.2608$) groups. Similarly, GOS scores differed significantly across groups ($F(2,125) = 7.54$, $P < 0.001$). Post-hoc comparisons showed that the TBI group (2.6 ± 0.7) had significantly higher GOS scores than the anoxic group (2.1 ± 0.5, $P < 0.001$), while the stroke group (2.4 ± 0.7) did not differ significantly from TBI ($P = 0.1557$) and anoxic ($P = 0.2282$) groups.

To further examine the association between demographic and clinical variables, we assessed correlations between age and both behavioral presentations and outcome measures. Age showed significant negative correlations with CRS-R scores ($r = -0.31$, $P < 0.001$) and GOS scores ($r = -0.39$, $P < 0.001$), indicating that younger patients were more likely to regain consciousness and achieve better functional recovery (Figure 1C). In contrast, time since injury was not significantly correlated with either CRS-R ($r = 0.09$, $P = 0.34$) or GOS scores ($r = -0.08$, $p = 0.34$). It suggests that injury duration did not independently predict consciousness level or recovery outcome in this cohort, all of whom had DoC lasting at least 28 days post-injury (Figure 1D). These findings are consistent with previous studies indicating limited prognostic value of injury duration.[37]

Relationships between clinical characteristics and functional connectivity

To investigate how clinical characteristics related to large-scale brain network organization in patients with DoC, we computed resting-state functional connectivity between all pairs of 22 cortical regions of interest, spanning six canonical cortical brain networks: default mode network, executive control network, salience network, sensorimotor network, auditory network; and visual network (Figure 2A).[19] Group-level comparisons identified twenty-five FCs with significant differences among anoxic, traumatic and stroke patients (one-way ANCOVA, $P < 0.05$, uncorrected; Figure 2B). These connections were distributed across all six brain networks, indicating widespread etiology-dependent alterations in functional connectivity patterns. We next assessed the relationship between demographic variables and brain connectivity. Eighteen FCs were significantly correlated with patients' age (Figure 2C), while eight FCs showed significant associations with time since

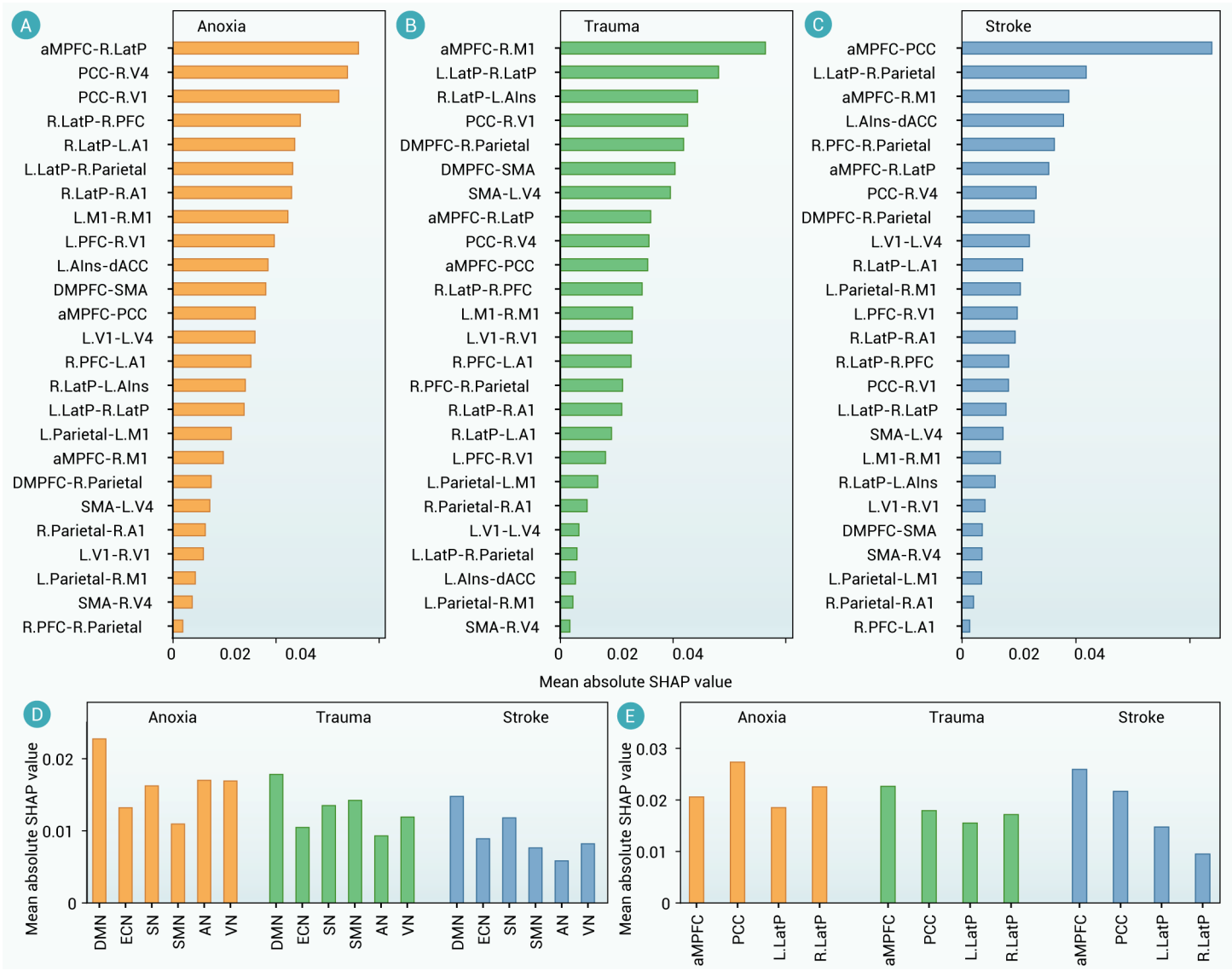


Figure 3. SHAP analysis of etiology-related functional connectivity features (A-C) Summary plots showing the mean absolute SHAP values for each functional connection, reflecting their relative contribution to predictive models of clinical variables: anoxia (A), trauma (B), and stroke (C). Higher SHAP values indicate greater importance in the classification model outputs. (D) Network-level rankings derived by averaging SHAP values across FCs within each brain network. (E) Node-level SHAP value ranking within the DMN.

injury (Figure 2D). All these clinical characteristics related network signatures were identified with scanner included as a covariate, demonstrating that the observed signatures were not primarily driven by scanner effects. To further strengthen the confidence in the robustness of these signatures, we applied the permutation-based sensitivity analysis. Results showed that all clinical characteristics associated FCs were robust against random variation (permutation test, $P < 0.05$, Figure S17). These exploratory clinical characteristics related FCs were used in the subsequent analyses.

We next examined the degree of overlap in FC patterns associated with different clinical characteristics (Figure 2E). The FC between the right prefrontal cortex (PFC) and left primary auditory cortex (A1) was shared between etiology- and age-related profiles. Similarly, the FC between the lateral parietal cortex (LatP) and dorsal medial PFC (DMPFC) overlapped between age- and time-associated FCs. Despite these localized overlaps, the majority of FCs were unique to a given variable (24/25 etiology-related FCs, 16/18 age-related FCs and 7/8 time-related FCs), supporting the conclusion that etiology, age, and time since injury associate with relatively independent patterns of functional connectivity.

Network ranking based on SHAP values

To identify brain network that carried most predictive information of distinct clinical characteristics, we applied SHAP analysis to machine learning models trained to predict etiology (anoxia, TBI, stroke), age, and time since injury, using all 231 FC features as inputs. Specifically, we built support vector classification (SVC) model to distinguish etiology (anoxia, trauma, stroke) and support vector regression (SVR) models to predict patient age and time since injury. The SVC model achieved a balanced accuracy of 0.44 and an AUC of 0.72 in discriminating among the three etiology types. In contrast, the SVR models for age and time since injury performed at chance level, yielding R^2 values of -0.23 and -0.15, respectively, with near-zero Pearson correlations (age: r = -0.04; time: r = -0.06). Given the poor performance of the SVR models, SHAP-based interpretation was performed only for the SVC model. In this model, SHAP values quantify the relative contribution of each FC to the model's predictions, with higher SHAP values indicating greater contributions to the classification decision. This enables identification of the connections most informative for discriminating among etiologies.

To assess feature reliability in the etiology SVC model, we computed the selection frequency of each FC across the 128 LOO folds (the proportion of folds in which the FC survived ANCOVA pre-selection). Applying a stringent threshold of 0.95, 25 FCs were consistently selected across folds (min = 0.9531), and this set was identical to etiology-related FCs that identified in the full-cohort ANCOVA. We focused SHAP analysis on these FCs (Figures 3A-C). Next, we grouped FCs according to their corresponding brain networks and computed the mean SHAP value across all FCs for each network. The

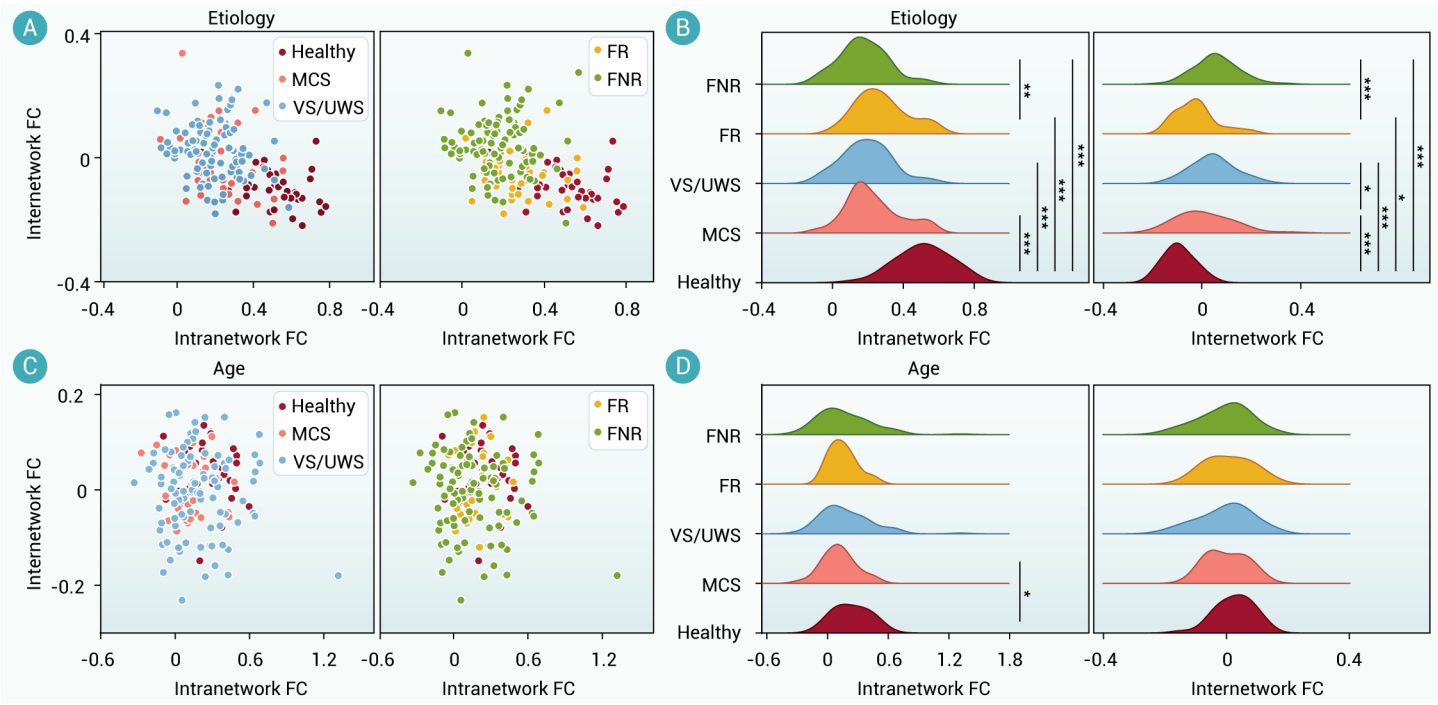


Figure 4. Intra- and internetwork functional connectivity in relation to consciousness level and functional recovery (A) Distributions of intra- and internetwork functional connectivity derived from etiology-associated connections across healthy controls, patients in a minimally conscious state (MCS) or vegetative state/unresponsive wakefulness syndrome (VS/UWS), and patients with or without functional recovery (FR, functional recovery; FNR, functional non-recovery). (B) Group comparisons of intra- (left) and internetwork (right) FC in relation to consciousness level and recovery status. (C-D) Similar analyses for FCs associated with patients' age, showing distributions (C) and group comparisons (D) for intra- and internetwork connectivity across diagnostic and recovery subgroups. Significant differences are indicated (* P < 0.05; ** P < 0.01; *** P < 0.001; FDR corrected; Mann-Whitney-Wilcoxon test).

network-level rankings revealed that the default mode network (DMN) exhibited the highest mean absolute SHAP value across all three etiology types (Figure 3D), suggesting that DMN connectivity carries the most predictive information for discriminating among etiologies. To further delineate the contribution of individual DMN nodes, we computed the mean absolute SHAP value for each of its four constituent ROIs: the anterior medial prefrontal cortex (aMPFC), posterior cingulate cortex/precuneus (PCC), and bilateral lateral parietal cortex (L.LatP and R.LatP). Notably, the PCC showed the highest mean absolute SHAP value for discriminating anoxia from the other etiologies, whereas the aMPFC exhibited the highest value for traumatic and stroke etiologies (Figure 3E).

Intra- and inter-network FCs and their relationships with consciousness and recovery

We further examined whether FC patterns associated with clinical characteristics were related to consciousness level and recovery. We categorized the 25 etiology-associated FCs into 9 intra-network and 16 inter-network connections and assessed their relationships with patients' consciousness level and functional recovery (Figure 4A). Compared to healthy controls, DoC patients exhibited disrupted intra- and inter-network connectivity. Specifically, patients showed lower intra-network FC (Figure 4B, all P < 0.05, FDR-corrected, Mann-Whitney-Wilcoxon test) and higher inter-network FC (P < 0.001 for patients in MCS, VS/UWS, FNR, P = 0.0167 for FR patients, FDR-corrected). Patients in the FR group showed more positive intra-network FC compared to that in the FNR group (Figure 4B, P < 0.01, FDR-corrected). Inter-network FC was significantly lower in FR patients than in FNR patients (p < 0.001, FDR-corrected). However, a marginal difference in inter-network FC between MCS and VS/UWS patients was observed (P = 0.0467, FDR-corrected). Collectively, these results suggesting that preserved within-network correlation and cross-network anticorrelation may support recovery of consciousness in DoC.

We next applied the same analytical approach to the age-associated FCs (Figures 4C-D) and time-associated FCs (Figure S18). Of the 18 age-related FCs, 2 were intra-network connections and 16 were inter-network connections. Among the 8 time-related FCs, no intra-network FCs were identified. Compared to healthy controls, only MCS patients showed marginal reduction in age-associated intra-network connectivity (Figure 4D, P = 0.0400, FDR-corrected). For the inter-network FCs associated with either age or time since injury, no significant differences were observed across groups (Figures 4D & S18). These results indicate that, unlike etiology-linked connectivity patterns, connectivity alterations associated with age or time since injury do not reliably differentiate current consciousness state or recovery outcome in DoC patients.

Together, these results suggest that intra- and inter-network FCs associated with etiology, but not age or injury duration, are closely linked to behavioral outcomes in DoC patients. Preserved modular network architecture, marked by strong intra-network correlation and inter-network anticorrelation, may serve as a neural signature of recovery potential.

Statistical mediation effect of functional connectivity

We conducted statistical path analyses to test whether the effects of clinical characteristics on patients' consciousness level and functional recovery outcomes were statistically mediated by intra- and inter-network FC. In these models, clinical characteristics were entered as the independent variables, intra- and inter-network FCs as the mediator variables, and consciousness level and functional recovery as the dependent variables. The goal of statistical path models was to quantify how much of the effect of a given clinical variable (X) on an outcome measure (Y) could be explained by indirect effect through functional connectivity, as opposed to the direct effect. Given that etiology is a multi-categorical variable, we adopted a dummy-coding approach: X_1 coded for traumatic brain injury (TBI), and X_2 for stroke, using anoxia as the reference group (coded as 0 on both X_1 and X_2) (Figure 5A).

We then evaluated the statistical mediating role of FC in relation to two outcome measures: consciousness level (CRS-R) and functional recovery (GOS). No significant indirect effects were observed in the models predicting CRS-R scores from etiology via intra- or inter-network FCs (Figure 5A). However, for GOS scores, an indirect effect was identified in TBI patients (X_1) via inter-network FC (Figure 5B). Specifically, the association between etiology (TBI relative to anoxia) and improved recovery outcomes was accounted for by an indirect effect through inter-network FC (a_1*b_1 = 0.0849, 95% CI:

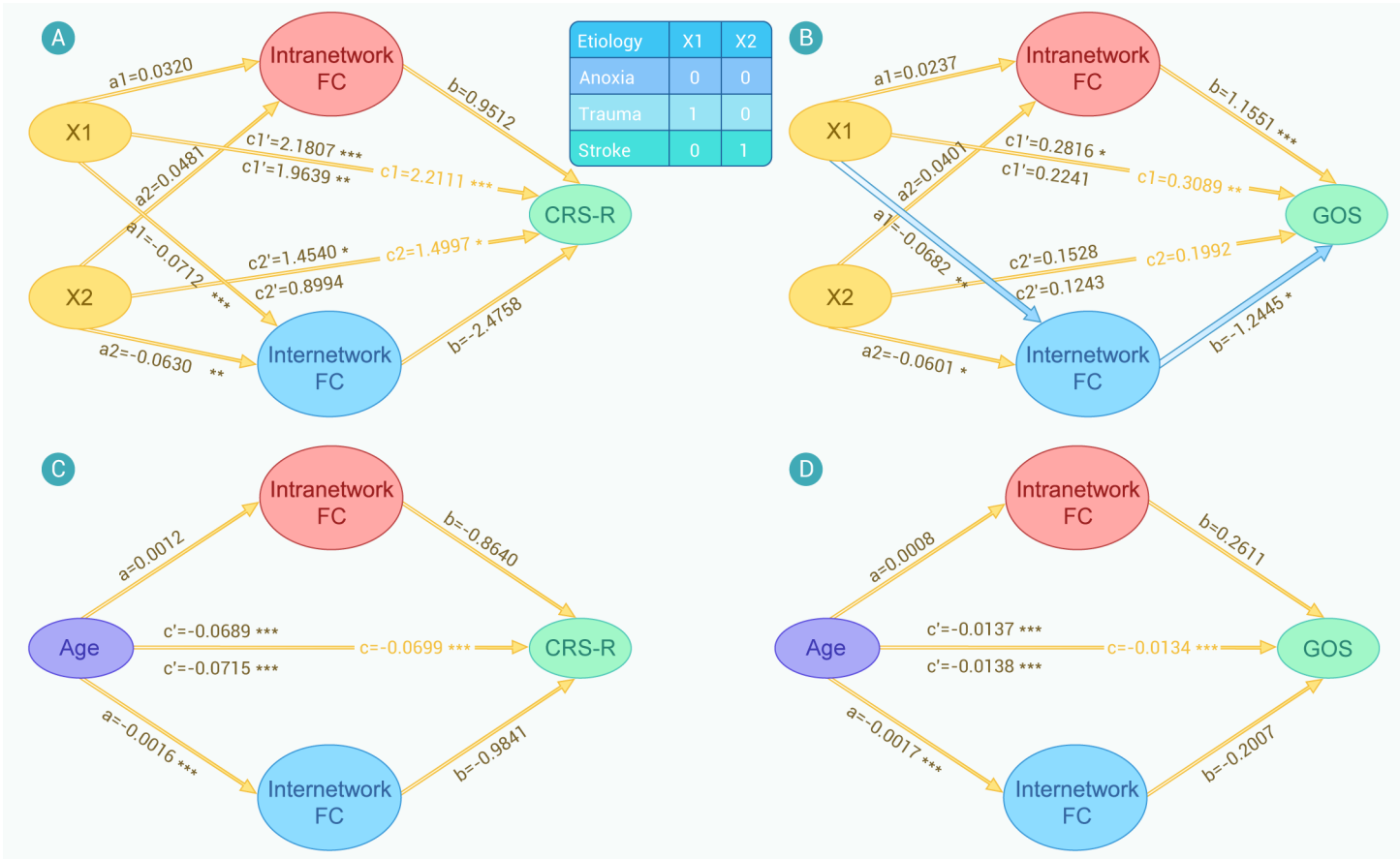


Figure 5. Mediation analysis linking clinical characteristics, functional connectivity, and behavioral outcomes (A) Mediation model testing whether the effect of etiology on consciousness level, measured by CRS-R, is mediated by intra- and inter-network functional connectivity. Etiology was dummy-coded with anoxia as the reference group (X_1 = trauma, X_2 = stroke). Path a_1/a_2 reflects differences in FC between traumatic/stroke and anoxic patients; path b captures the association between FC and CRS-R scores; path c' indicates the direct effect of etiology on CRS-R; and the total effect (path c) includes both direct and indirect contributions via FC. (B) A similar mediation model examining the relationship between etiology and functional outcome (GOS), with FC as a mediator. Significant indirect effects via inter-network functional connectivity (blue lines) were observed for traumatic versus anoxic injuries. (C-D) Mediation analyses testing whether the effect of patient age on CRS-R (C) and GOS (D) is accounted for by intra- and inter-network FC. Effect sizes are shown along each path; red text indicates intra-network FC pathways, and blue text indicates inter-network FC pathways. Significant paths are denoted by * P < 0.05, ** P < 0.01, *** P < 0.001 (t-test).

0.0083 to 0.2160). These results suggest that alterations in inter-network connectivity could accounted for the beneficial impact of traumatic etiology on functional recovery.

We also examined whether the age-outcomes association was explained by functional connectivity (Figures 5C-D). Although age showed significant direct negative effects on both CRS-R and GOS scores, indicating that older patients tended to have poorer consciousness levels and outcomes, these effects were not explained by intra- or inter-network FCs. Given the lack of time since injury related intra-network FC, we conducted path analysis for inter-network FC. No significant indirect effects were found for time since injury on either CRS-R or GOS scores (Figure S19).

Together, these results highlight that among the examined clinical variables, etiology, specifically TBI versus anoxia, contribute to functional recovery through an FC-explained statistical pathway. This underscores the relevance of inter-network connectivity as a potentially important intermediate variable in the association between injury type and outcome in patients with DoC.

DISCUSSION AND CONCLUSIONS

In this study, we demonstrate that clinical characteristics, particularly etiology, age, and time since injury, are not only behaviorally relevant in disorders of consciousness (DoC), but also exert selective and dissociable associations with large-scale brain network architecture. By integrating clinical neurobehavioral assessments, clinical characteristics, and resting-state functional connectivity analyses in a relatively large cohort of 128 DoC patients, we reveal that the heterogeneity of clinical presentation is mirrored by distinct connectivity profiles, and that some of these patterns, particularly those linked to etiology, statistically account for recovery outcomes.

Previous network studies have predominantly focused on the association between functional connectivity and patients' consciousness levels and functional recovery.[19,21-27,38] The current study extends this perspective by examining how clinical characteristics relate to functional connectivity in DoC patients. Our findings revealed that clinical characteristics, including etiology, age, and time since injury, are associated with distinct and largely non-overlapping patterns of large-scale brain cortical connectivity, reflecting independent axes of network reorganization in disorders of consciousness. Minimal overlap between the FCs associated with these variables, such as the $FC_{R.PFC-L.A1}$ for both etiology and age, and the $FC_{L.LatP-DMPFC}$ for both age and time since injury, underscores their separable neurobiological substrates. However, a critical boundary condition of this study is that our functional connectivity analyses were derived exclusively from 22 cortical ROIs, without including subcortical structures such as the thalamus, brainstem, or basal ganglia. These regions are unequivocally central to the maintenance and recovery of consciousness.[9,39-41] Future studies integrating high-resolution imaging or animal models with targeted recordings of these regions will be essential to offer a more comprehensive understanding of the neural substrates underlying DoC.

Using SHAP-based model interpretation, we identified the DMN as the top-ranked network across all three etiology types. The brain networks for age and time since injury were not identified, given the poor SVR models performance. Alterations in DMN have been widely reported in DoC patients and are closely linked to patient's consciousness level and functional recovery.[21-24,27] Our findings further indicated that DMN connectivity carries the greatest discriminative information for distinguishing among etiologies. This suggested that alterations in DMN connectivity might exhibit the most

pronounced differences across injury types relative to other large-scale networks in our model. At the ROI level, the PCC and aMPFC showed dissociable contribution patterns: the PCC exhibited the highest SHAP value for anoxia, whereas the aMPFC showed the highest values for trauma and stroke. This node-level dissociation suggested that different subnetworks within the DMN might capture etiology-related information in differential ways—a possibility that warrants further investigation.

Building on previous work showing that intra- and inter-network connectivity can reflect consciousness states,[38,42] we found that patients who achieved functional recovery exhibited higher intra-network FC and lower inter-network FC than non-recovered patients. These patterns align with previous research finding[42] and were specifically derived from FCs associated with etiology, but not from those related to age or time since injury. These results suggest that only certain dimensions of clinical heterogeneity are associated with functionally relevant network reorganization. Importantly, preserved intra-network correlation and inter-network anticorrelation may reflect network modularity,[43] a key property for efficient information processing and flexible cognitive control. Similar modularity has been reported in other conditions with consciousness or cognitive impairment, including Alzheimer's disease,[44] epilepsy,[45] and dementia with Lewy bodies.[46] The replication of this modular architecture in DoC patients with favorable outcomes reinforces the potential of network modularity as a cross-diagnostic biomarker for recovery capacity.

Our statistical path analyses further revealed that only etiology, not age or time since injury, exerted an indirect effect on recovery outcomes through functional connectivity. Specifically, inter-network connectivity accounted for the beneficial effect of traumatic etiology on functional outcome, in line with the notion that dynamic switching between brain networks is critical for conscious cognition.[38] Notably, this indirect effect was statistically significant, whereas the direct path from etiology to recover outcomes was not significant (Figure 5B, $c1' = 0.2241$, $P > 0.05$). Critically, these effects were robust to adjustment for multiple potential confounders, including age, diagnosis, scanner, and head motion, reinforcing the validity of our findings. These results highlight that functional network architecture is not merely an epiphenomenon, but a significant statistical pathway linking etiology to recovery. Age did not show a similar statistical mediating effect, implying that the prognostic pathways of age and etiology may be dissociable, with age likely relating to recovery through other systemic mechanisms.

While this study benefits from a relatively large and well-characterized patient cohort and leverages clinical, neurobehavioral and imaging data acquired during routine clinical care, several limitations should be considered. First, the heterogeneity in MRI data acquisition. Our analyses incorporated data from multiple scanners with varying parameter sets, which may introduce scanner-related variability into FC estimates.[47] We included scanner as a covariate in all statistical models to minimize its confounding effects. Our results showed that the etiology-related network signatures were unlikely to be primarily driven by scanner effects. However, this correction may not fully account for all scanner-specific influences on connectivity metrics. Future multi-site studies with standardized protocols are warranted to further validate our findings. Second, our focus on static FCs does not capture dynamic aspects of network organization. Incorporating dynamic FC metrics[28,48] and advanced graph-theoretical approaches[49] may provide deeper insight into the temporal variability and integrative capacity of brain networks. Third, the mediating role of inter-network FC would need to be interpreted with great caution, as brain structural lesion might independently contribute to both FC changes and poor recovery. The statistical pathway dose not provide direct evidence for a causal interpretation of the mediation. We emphasize that future longitudinal studies with repeated FC measures are needed to establish temporal precedence. Additionally, animal models could offer a complementary approach to further investigate this pathway, although establishing models that adequately represent distinct DoC etiologies is challenging. If feasible, such models could be combined with neuromodulation techniques to test whether targeted modulation of inter-network connectivity influences recovery-related outcomes, which would provide stronger evidence for the role of this pathway.

In summary, the present study demonstrates that clinical characteristics, especially etiology and age, are associated with anatomically specific and functionally meaningful alterations in large-scale brain network connectivity. Notably, etiology was found to associate with recovery outcomes indirectly via inter-network connectivity, highlighting a potential statistical pathway linking clinical context to functional prognosis. Overall, these findings underscore the value of integrating neuroimaging biomarkers with clinical profiling to improve prognostic accuracy and inform the development of individualized therapeutic strategies for patients with prolonged disorders of consciousness.

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AUTHOR CONTRIBUTIONS

Huan Wang: Conceptualization, Methodology, Investigation, Visualization, Funding acquisition, Writing—original draft, Writing—review & editing. Qianqian Ge: Data curation. Shuai Han: Data curation. Kaitian Chen: Data curation. Aoxuan Liu: Data curation. Qiuyou Xie: Data curation. Peng Zhang: Writing—review & editing. Sheng He: Writing—review & editing. Jianghong He: Data curation. Yan Yang: Conceptualization, Funding acquisition, Supervision, Writing—original draft, Writing—review & editing. All authors read and approved the final version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

Ethical approval was obtained from the Ethics Committee of the PLA Army General Hospital (protocol No: 2011-097 and 2011-0415) and the Ethics Committee of Guangzhou General Hospital of Guangzhou Military Command (protocol No: jz20091287). Informed consent was obtained from legal guardians of patients and from healthy control participants in accordance with institutional guidelines.

DATA AND CODE AVAILABILITY

Datasets supporting the findings of this study are available from the corresponding author on reasonable request. Codes for fMRI processing are available at https://github.com/elifesciences-publications/pDOC.

SUPPLEMENTAL INFORMATION

It can be found online at https://doi.org/10.59717/j.xinn-life.2026.100266.