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Functional networks in auditory perception provide fingerprints for accurate diagnostic assessment of disorders of consciousness: a fNIRS study

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Abstract

Disorders of consciousness (DoC) are primarily diagnosed using behavioral assessments, which are prone to high misdiagnosis rates. Objective neural markers are therefore needed. This study investigated residual neural responses to naturalistic auditory stimuli in DoC patients to better reflect covert consciousness. Four auditory conditions were presented: natural speech sentences, music, animal sounds, and pure tones as a baseline. Functional near-infrared spectroscopy (fNIRS) was used to assess cortical activation, hemodynamic responses, and functional network alterations during auditory processing. A support vector machine (SVM) classifier was applied to distinguish vegetative state (VS) from minimally conscious state (MCS) patients and to identify the most informative neural features. Complex natural stimuli, particularly speech and music, elicited more specific hemodynamic and network responses than pure tones. Patients with higher consciousness levels showed selectively enhanced left-hemispheric activity and stronger long-range network connectivity during speech perception. The model achieved an overall accuracy of 86.84% (VS: 78.57%; MCS: 91.67%), with the top contributing features exclusively network-based. These findings support the value of naturalistic auditory paradigms and network features for precise DoC assessment.

Keywords: disorders of consciousness; fNIRS; functional network; auditory processing

Introduction

Disorders of consciousness (DoC) are severe neurological conditions, including the vegetative state (VS), the minimally conscious state (MCS). VS is characterized by wakefulness without signs of self- or environmental awareness, whereas MCS is marked by inconsistent but reproducible behavioral evidence of conscious awareness (Bruno et al., 2011). The transition to the emergence from the minimally conscious state (EMCS) is marked by the recovery of functional communication. Accurate classification among these states is vital for prognosis and personalizing rehabilitation strategies.

Current clinical diagnosis of DoC primarily relies on the Coma Recovery Scale-Revised (CRS-R), which assesses consciousness through overt motor responses to commands (Giacino et al., 2004). However, a fundamental limitation of this approach is its inability to detect cognitive-motor dissociation (CMD), where damaged motor pathways prevent patients from externally expressing their preserved internal cognitive functions (Bodien et al., 2024). Studies indicate that up to 15-25% of patients diagnosed as VS via behavioral scales actually demonstrate covert awareness in neuroimaging tasks (Bodien et al., 2024; Kondziella et al., 2016; Monti et al., 2010). The failure to capture the residual consciousness serves as a primary driver of the high misdiagnosis rate, which reaches up to 40% in traditional clinical assessments (Owen, 2019). Such misdiagnosis may delay appropriate treatment and rehabilitation planning, thereby imposing a substantial burden on patients ’ families and society (Tinti et al., 2024; Wannez et al., 2017). Consequently, the development of objective, non-invasive, and efficient diagnostic approaches has become a major focus in this field.

To bypass the limitations of behaviral evaluations, researchers have turned to neurofunctional assessments. Although functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) have been reported to be capable of identifying CMD (Cruse et al., 2011; Monti et al., 2010; Owen et al., 2006), their clinical application is often hindered by patient-related involuntary movements and environmental noise in intensive care settings. In light of these challenges, functional near-infrared spectroscopy (fNIRS) has emerged as a promising alternative. As a non-invasive, portable, and motion-tolerant neuroimaging tool (Ferrari & Quaresima, 2012), fNIRS is uniquely suited for bedside assessment of residual cognitive function.

While previous studies in DoC have largely relied on active tasks such as motor imagery (Goldfine et al., 2011; Kempny et al., 2016; Monti et al., 2010), these paradigms impose high cognitive demands that often exceed the capabilities of many patients. In contrast, passive auditory processing paradigms may offer a more reliable way to detect residual consciousness by eliciting automated neural responses. Recent studies have shifted focus toward the presentation of naturalistic auditory stimuli commonly encountered in daily life (Gao et al., 2025; Hu et al., 2021; Luo et al., 2024), such as spoken sentences and music, due to their high ecological validity. Moreover, neural responses to such familiar, daily-life stimuli may better reflect a patient ’ s residual cognitive function (Lu et al., 2023) and are more likely to engage wide-spread networks due to their acoustic complexity. Consequently, such naturalistic

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paradigms enable more accurate differentiation among DoC subtypes.

In addition to speech and music, this study introduced animal vocalizations as a critical intermediate stimulus, a category rarely explored in DoC research. From a functional hierarchy perspective, animal vocalizations occupy a unique position: they require the brain to bridge sound and simple semantic representations (sound-to-meaning association) similar to speech, yet they lack its complex acoustic and syntactic structures. By comparing neural responses across a gradient of complexity ranging from the fundamental pitch analysis of pure tones and the intermediate semantic decoding of animal vocalizations to the sophisticated emotional and linguistic integration of music and speech, this hierarchical design enables a fine-grained assessment of residual cognition across different DoC patients.

With an appropriate assessment paradigm, the robustness of clinical classification depends on the integration of multidimensional neural markers. To avoid the limitations of single-feature analyses, which often struggle to capture the complex neurofunctional variability inherent in DoC populations and lead to inconsistent diagnostic outcomes (Giacino et al., 2014; Kondziella et al., 2020), recent advancements emphasize multi-feature fusion. This approach integrates various neural indices, most notably functional connectivity, which reflects the coordination between distant cortical networks. By employing machine learning algorithms to synthesize these diverse neural signatures, it becomes possible to construct objective diagnostic models that outperform traditional univariate approaches (Bella et al., 2025; Gui et al., 2020). Such an integrated approach not only enhances the sensitivity of detecting residual consciousness but also provides a more stable framework for the automated differentiation of DoC subtypes in clinical practice.

Overall, the present study utilized fNIRS to examine residual neural responses to diverse naturalistic auditory stimuli in 48 DoC patients (comprising14 VS, 24 MCS, and 10 EMCS), with the following objectives: (1) to characterize neural response patterns to naturalistic auditory stimulation between DoC and healthy controls (HC), and among VS, MCS, and EMCS patients; and (2) to employ a machine-learning framework to reliably differentiate DoC subtypes and identify the neural features that best index the degree of consciousness. Ultimately, this study aims to support the development of a precise, bedside neuroimaging approach for DoC classification, with potential implications for optimizing clinical interventions and healthcare resource allocation.

Method

Participants

A total of 48 DoC patients were enrolled (M_{age} = 49.83 yrs, SD = 15.70; 15 females), including 14 VS patients, 24 MCS patients, and 10 EMCS patients. All DoC patients were diagnosed based on the Chinese versions of the CRS-R (Di et al., 2017; Giacino et al., 2004). In addition, 36 healthy control participants were recruited (M_{age} = 41.42 years, SD = 15.64; 24 females). The control group primarily consisted of age-matched family members of the patients, helping to reduce potential confounding related to background factors. Healthy controls had no history of neurological or psychiatric disorders. Written informed consent was obtained from all healthy participants and from the legal guardians of DoC patients.

Stimuli

Four types of auditory stimuli were used in this study to probe residual auditory and cognitive processing at different levels of representational complexity. Naturalistic stimuli were selected to better approximate real-world listening conditions and to increase the likelihood of engaging preserved high-level auditory and cognitive processes in DoC patients.

The first condition consisted of natural Chinese utterances composed of five characters that are commonly used in daily communication (e.g., "Tʰa55 mən35 tsai51 kʰan51 ʂu55", meaning "They are reading books"). The second condition included modulated 440-Hz pure tones that were matched to the pitch contour, duration, and loudness of the sentences used in the first condition. This manipulation aimed to remove syntactic and semantic information while preserving key phonological and prosodic characteristics of the original speech stimuli (Plante et al., 2006; Song et al., 2016). The third condition comprised auditory segments of animal vocalizations (e.g., dog barking). The fourth condition consisted of instrumental music without lyrics. Each condition included 15 trials, and in each trial the auditory stimulus lasted for 2 s.

Procedure

After receiving a detailed explanation of the experimental procedure, participants were seated in a quiet, electrically shielded room. Hemodynamic responses were recorded using a multichannel fNIRS system (LIGHTNIRS; Shimadzu Co., Ltd., Tokyo, Japan). Sixteen optodes were arranged in two 2 × 4 arrays (each comprising four sources and four detectors) and symmetrically positioned over the bilateral fronto-temporal regions, primarily covering cortical areas adjacent to the lateral fissure, including the inferior frontal gyrus (pars opercularis, BA44), superior temporal gyrus (STG, BA22), middle temporal gyrus (MTG, BA21), and supramarginal gyrus (SMG, BA40).

Participants were instructed to remain still and to listen attentively to the auditory stimuli, with no overt behavioral response required. The auditory perception task employed a slow event-related design (Aarabi et al., 2017), in which each 2-s auditory stimulus was followed by a 10-s rest interval. Auditory stimuli were delivered in a randomized order via loudspeakers at 75 dB. The experiment was programmed using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA, USA), and the total duration of the fNIRS session was approximately 12 min.

Data Analysis

All fNIRS data were first preprocessed using the HomER toolbox, including removal of poor-quality channels, correction for motion artifacts, bandpass filtering (0.01–0.1 Hz), and detrending. After preprocessing, the fNIRS data were then analyzed through three complementary approaches: cortical activation detection, characterization of HbO signal changes, and functional network analysis. In addition, multivariate classification models were constructed to evaluate the predictive value of fNIRS-derived features.

Cortical Activation Given that HbO provides higher sensitivity to task-related hemodynamic changes than deoxyhemoglobin, activation analyses focused on HbO signals. Cortical activation under different auditory conditions was estimated using a general linear model (GLM) implemented in NIRS-SPM (version 3) and SPM8 (Ye et al., 2009). The HbO time series was modeled using a canonical hemodynamic response function, and beta coefficients were extracted to quantify task-related activation at each channel.

Time-series analysis of HbO changes To examine the temporal dynamics of hemodynamic responses, grand-averaged HbO time courses were computed for each condition based on the preprocessed data. Based on the canonical hemodynamic response profile, two post-stimulus time windows were defined: an early processing window (2-6 s) and a late processing window (6-10 s). Mean HbO values were extracted within each window for each condition. Group-level differences in these window-averaged HbO responses were assessed using non-parametric Mann-Whitney U tests. To account for multiple comparisons across conditions and time windows, p-values were corrected using the false discovery rate (FDR) procedure. Results were considered statistically significant after FDR correction at $q < 0.05$.

Functional network analysis Functional connectivity was evaluated using HbO signals by constructing connectivity matrices for each condition. Three complementary connectivity measures were computed to characterize functional network organization: Pearson correlation, magnitude-squared coherence, and phase locking value (PLV), capturing temporal correlation, frequency-domain coupling, and phase synchronization between channels, respectively.

Classification and feature stability analysis To evaluate the discriminative value of fNIRS-derived features, support vector machine (SVM) classifiers were constructed to distinguish VS from MCS. Features included condition-specific activation values, HbO values, and functional connectivity metrics derived from correlation, coherence, and PLV analyses. For each subject, these features were organized into subject-level feature vectors. Prior to classification, feature values were standardized using z-score normalization within each training fold.

Classification performance was evaluated using a leave-one-subject-out cross-validation scheme. Feature selection was performed within each training fold using ANOVA-based ranking. Model performance was assessed using classification accuracy (ACC) and the area under the receiver operating characteristic curve (AUC).

To examine the robustness of feature selection, feature stability was evaluated by aggregating feature rankings across all cross-validation folds. Specifically, the mean ranking position of each feature across folds (MeanRank) and its frequency of appearance among the top-ranked features (FreqInTopK; top 10 features per fold) were calculated, providing an index of consistently informative features for distinguishing VS from MCS.

Result

Selective sensitivity to complex naturalistic auditory stimuli in disorders of consciousness

We first compared neural responses between the DoC and HC during the processing of four naturalistic auditory stimuli. During the early processing stage of speech, as shown in Fig.1a, HbO responses in the left frontal pole (CH7) were significantly higher in HC than in DoC (p_{FDR} = 0.0608; $q < 0.05$). In contrast, during the early processing stage of music, DoC showed significantly higher HbO responses than HC in the dorsolateral prefrontal cortex and frontal pole (CH3, $p_{FDR} = 0.0026$), as well as in the right supramarginal and angular gyri (CH46, $p_{FDR} < 0.001$). No significant group differences were observed in the other conditions. These results indicate that the most pronounced differences between DoC and HC emerged during the processing of more complex auditory stimuli.

Within the DoC group, neural responses further varied across subtypes. Overall, stronger HbO responses to music were associated with milder DoC, with graded increases from VS to MCS and to EMCS, particularly in the right SMG (CH44, all $p_{FDR} < 0.001$). During the early stage of speech processing, HbO responses in the left SMG (CH11) and AG (CH14) increased with decreasing severity of consciousness impairment, showing higher activity in MCS than in VS and in EMCS than in MCS (all $p_{FDR} < 0.05$), as shown in Fig. 1b. In contrast, pure tones and animal sounds elicited weaker and less differentiated responses: no group differences were observed during the early processing stage, whereas during the late stage, more severe consciousness impairment was associated with stronger HbO responses in the left AG for pure tones and in the right SMG for animal sounds. Together, these findings indicate that more complex naturalistic auditory stimuli, such as music and speech, evoke more specific and severity-dependent neural responses in DoC, supporting their potential value for clinical classification.

In addition, we examined neural network patterns underlying auditory processing in DoC. Compared with HC, DoC showed markedly disrupted auditory networks, especially during speech and music perception, characterized by fewer strong connections (PLV > 0.75) and a lack of long-range interhemispheric connectivity. During both speech and music perception, HC exhibited dense within-region connectivity together with long-range connections linking prefrontal regions to the right angular gyrus and across hemispheres, whereas these network features were largely absent in DoC patients. These results indicate that impaired network organization is a prominent neural hallmark of DoC.

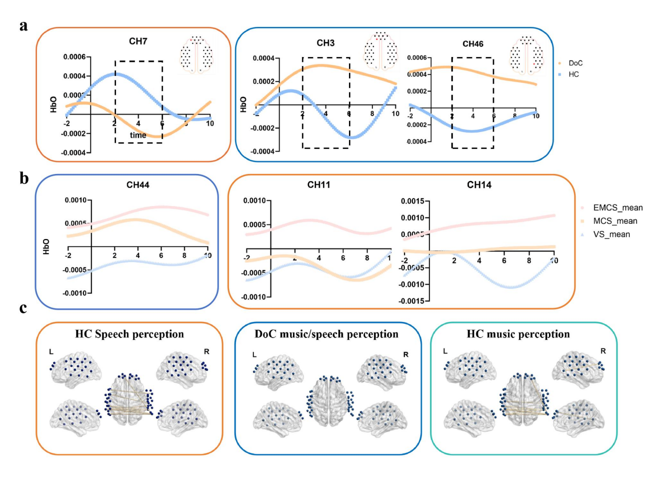

Figure 1: a Comparison of hemodynamic responses between DoC and HC. The orange box indicates the speech perception condition, and the blue box indicates the music perception condition. Dashed boxes mark time windows showing significant hemodynamic differences. **b** Comparison of hemodynamic responses among VS, MCS, and EMCS. The orange box indicates the speech perception condition, and the blue box indicates the music perception condition. **c** Functional network connectivity in DoC patients and HC during speech and music perception. Blue dots represent cortical regions of interest, and yellow edges represent strong connections. HC exhibit widespread long-range connectivity under both speech and music conditions, whereas this network characteristic is markedly reduced in patients.

Differences in auditory network organization were further evident across DoC subtypes. During speech perception, patients with more severe DoC showed a higher number of strong connections (VS: 41 pairs; MCS: 26; EMCS: 17, Fig. 2a), whereas the strength of a key long-range connection between the dorsolateral prefrontal cortex and the right AG increased with milder consciousness impairment (VS: PLV = 0.659; MCS: 0.676; EMCS: 0.689). During music perception, a similar increase in the number of strong connections was observed in patients with more severe disorders of consciousness (VS: 34; MCS: 25; EMCS: 29, Fig. 2b), while the key dorsolateral prefrontal-right angular gyrus connection was stronger in VS than in MCS (VS: PLV = 0.680; MCS: 0.670). Together, these results further support a selective modulation of auditory network organization by complex auditory stimuli across different DoC.

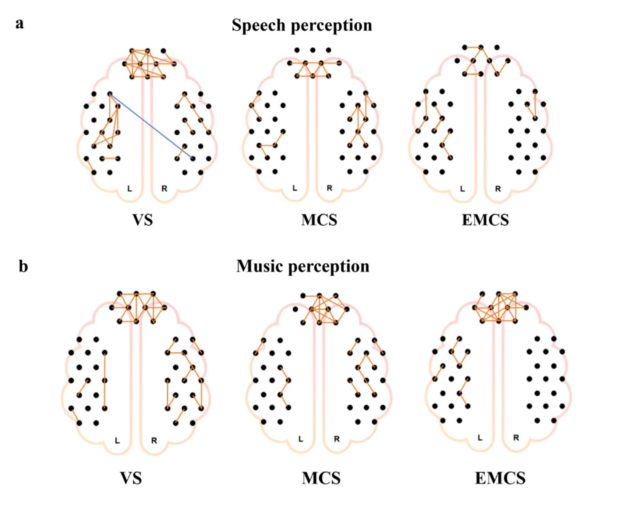

Figure 2: a Under the speech perception condition, patients with lower levels of consciousness exhibited a greater number of strong connections. Orange lines indicate strong intra-regional connections within frontal or temporal areas, whereas blue lines represent long-range inter-regional connections. **b** Under the music perception condition, patients with lower levels of consciousness also showed a greater number of strong connections.

Network features under naturalistic auditory stimulation best predict patient classification

To determine whether neural responses to natural auditory processing can reliably distinguish between DoC subtypes, we evaluated the classification performance of multiple neural features—including activation measures, HbO signals, and functional connectivity metrics (correlation, coherence, and PLV)—using an SVM classifier. The SVM achieved an overall classification accuracy of 86.84% (Fig. 3a) with an AUC of 0.9003, indicating robust discriminative performance between VS and MCS. Class-wise analysis showed a classification accuracy of 78.57% for VS and 91.67% for MCS, suggesting higher sensitivity in identifying patients with relatively preserved consciousness.

To identify the neural features that most accurately distinguish DoC subtypes, we applied ANOVA-based feature selection across all training folds and identified the ten most stable and discriminative features (Fig. 3b). Notably, all selected features were functional connectivity measures (coherence, PLV, and correlation) derived from speech, pure ton, animal vocalization, and music perception, whereas neither activation β values nor HbO features appeared among the top ten. This pattern indicates that network-level features under naturalistic auditory stimulation provide stronger discriminative information for differentiating DoC subtypes.

Among these features, three connections were consistently selected in the top ten across all 38 training folds (Fig. 3c): coherence between the frontopolar area

(BA10) and the right visual association cortex V3 (BA19) during animal sound perception, PLV between the left primary and auditory association cortex (BA42) and the right angular gyrus (BA39) during speech perception, and coherence between the dorsolateral prefrontal cortex (BA9) and the right MTG (BA21) during music perception. Importantly, the coherence between the frontopolar area and the right V3 during animal sound perception was ranked first on average in every feature selection iteration, suggesting that it most robustly differentiates VS from MCS. Together, these findings further indicate that, compared with simpler auditory stimuli such as pure tones, more complex auditory stimuli (speech, animal sounds, and music) exert stronger and more reliable modulatory effects on neural networks associated with the level of consciousness.

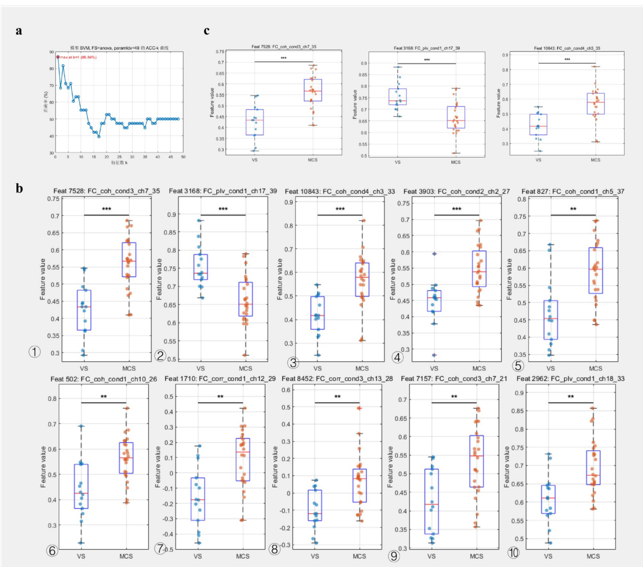

Figure 3: a Classification performance of the SVM model based on auditory processing–related neural features, achieving an overall accuracy of 86.84% in discriminating VS from MCS patients. **b** The ten most stable and discriminative features identified by feature selection across cross-validation folds. Blue dots represent VS subjects, and orange dots represent MCS subjects. **c** Three functional connections were consistently selected among the top ten features across all 38 training folds, indicating robust and reproducible discriminative patterns.

Discussion

In this study, we used fNIRS to investigate neural responses to naturalistic auditory stimuli in DoC patients across activation, hemodynamic, and network levels. Three main findings emerged. First, complex stimuli such as speech and music elicited stronger and more discriminative neural responses than simple stimuli, with response magnitudes in prefrontal and temporoparietal regions scaling with residual consciousness from VS to MCS to EMCS. Second, DoC patients showed disrupted auditory functional networks, particularly reduced long-range interhemispheric connectivity between prefrontal regions and the right angular gyrus. Third, functional connectivity features provided the most reliable basis for classification, yielding 86.84% accuracy (AUC = 0.90) in distinguishing VS and MCS. These results suggest that task-evoked functional networks under naturalistic stimulation can serve as robust neural markers for bedside assessment of consciousness.

Selective sensitivity to complex naturalistic auditory stimuli in disorders of consciousness

Stimulus complexity emerged as a key factor in differentiating DoC subtypes. Compared with pure tones and animal sounds, speech and music elicited more clearly graded neural responses. HbO responses increased stepwise with milder DoC for complex stimuli, whereas simpler stimuli produced weaker and less discriminative effects. At the network level, complex stimuli revealed systematic changes in long-range connectivity that were largely absent under simple conditions. This advantage is consistent with the higher ecological validity of naturalistic stimuli and their ability to capture real-life auditory processing (Moerel et al., 2012; Sonkusare et al., 2019).

This pattern can be understood within a hierarchical framework of auditory processing. Simple stimuli mainly engage early sensory regions, which are relatively preserved even in severe DoC (Laureys et al., 2000; Boly et al., 2011), limiting their discriminative value. In contrast, complex stimuli recruit higher-order processes such as semantic integration, temporal prediction, and affective processing, which depend on large-scale prefrontal and temporoparietal networks (Hickok & Poeppel, 2007; Koelsch, 2014). Because consciousness relies on such integrative processing rather than early sensory responses alone, complex stimuli are more effective for probing residual functional organization (Dehaene & Changeux, 2011; Tononi et al., 2016).

Within the DoC group, neural responses showed graded differences aligned with consciousness level. During music perception, HbO responses in the right supramarginal gyrus increased from VS to MCS to EMCS, while during early speech processing similar patterns appeared in left supramarginal and angular gyri. This lateralization (right for music, left for speech) is consistent with known hemispheric specialization (Zatorre et al., 2002; Hickok & Poeppel, 2007), indicating that these responses reflect stimulus-specific higher-order processing rather than nonspecific arousal. The involvement of supramarginal and angular gyri — key nodes of the inferior parietal lobule and default mode network — further supports their role in conscious awareness (Vanhaudenhuyse et al., 2010; Seghier, 2013).

One notable finding was that DoC patients showed stronger early-stage HbO responses than healthy controls in prefrontal and temporoparietal regions during music processing. Similar hyperactivation patterns have been reported in DoC and related conditions, and are often interpreted as compensatory or inefficient recruitment due to impaired top-down regulation (Di Perri et al., 2013; Crone et al., 2014).

Disrupted long-range functional networks as a neural hallmark of DoC

At the network level, DoC patients exhibited fewer strong functional connections overall and a marked loss of long-range interhemispheric connectivity, particularly between prefrontal regions and the right angular gyrus. Importantly, the strength of this connection increased with milder consciousness impairment, suggesting that it tracks the depth of residual consciousness. Similar connectivity disruptions have been widely reported across large-scale networks in DoC (Demertzi et al., 2015; Naro et al., 2018; Wang et al., 2025).

This pattern aligns with leading theories such as the Global Neuronal Workspace and Integrated Information Theory, which emphasize large-scale integration as a basis of conscious processing (Dehaene & Changeux, 2011; Tononi et al., 2016). The weakening of long-range prefrontal−parietal coupling may therefore represent a core neural mechanism underlying impaired consciousness.

Interestingly, the total number of strong connections showed an inverse relationship with consciousness level, with VS patients exhibiting more connections than MCS and EMCS. This counterintuitive pattern likely reflects pathological hypersynchrony and reduced functional differentiation rather than efficient processing, as suggested in previous studies (Fingelkurts et al., 2012; Demertzi et al., 2019). Thus, the network signature of DoC depends more on the specificity and organization of connections than on their overall quantity.

Functional network features provide robust neural fingerprints for DoC classification

Building on these findings, machine-learning analyses demonstrated that functional connectivity provides robust neural fingerprints for DoC classification. Using an SVM classifier, we achieved 86.84% accuracy in distinguishing VS from MCS, with all top discriminative features derived from connectivity measures rather than activation or HbO responses. This supports the view that consciousness is fundamentally a network-level phenomenon (Dehaene & Changeux, 2011; Tononi et al., 2016).

Clinically, this approach offers several advantages. It is passive, requires no behavioral response, and can be implemented at the bedside using portable fNIRS, making it suitable for severely impaired patients. Compared with traditional behavioral assessments that are prone to misdiagnosis (Schnakers et al., 2009) and active neuroimaging paradigms with high demands on patient cooperation (Monti et al., 2010; Owen, 2019), this framework provides a practical pathway toward more accurate and individualized DoC assessment.

Clinical implications, limitations, and future directions

Several limitations should be noted. The sample size, particularly for EMCS, was relatively small. fNIRS is limited to cortical regions and cannot assess deeper structures such as the thalamus, which are critical for consciousness (Laureys et al., 2000; Edlow et al., 2021). The cross-sectional design precludes conclusions about prognosis, and patient etiology was not systematically controlled.

Future research should include longitudinal studies to evaluate prognostic value and explore stimulus-specific intervention strategies. The differential effects of speech and music suggest that tailored auditory stimulation may support individualized neurorehabilitation.

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