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Prospects for the Application of Neural Oscillations in the Diagnosis and Treatment of Disorders of Consciousness (Postprint)

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Abstract

The diagnosis and treatment of Disorders of Consciousness (DOC) present considerable challenges, with disruption of neural oscillation synchronization and connectivity representing one of the key neural mechanisms underlying DOC. This article reviews the research progress of neural oscillations in DOC diagnosis and treatment from three perspectives: theoretical foundations, application advances, and existing limitations. Neural oscillations are defined as periodic, synchronous firing activities generated by neuronal populations under specific conditions. In DOC of varying severity, significant differences are observed in the spectral characteristics, phase synchronization, and responses to neuromodulation of neural oscillations. EEG-based neural oscillation analysis reveals information transmission and processing capabilities across different consciousness levels, thereby facilitating more accurate differentiation of varying degrees of DOC and enabling arousal therapy through modulation of neural oscillations. Despite current challenges such as insufficient mechanistic research and slow translational application, neural oscillations have demonstrated tremendous potential in the diagnosis and treatment of DOC.

Full Text

Perspectives on the Application of Neural Oscillations in the Diagnosis and Treatment of Consciousness Disorders

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Abstract

The diagnosis and treatment of disorders of consciousness (DOC) remain challenging, with disrupted synchronization and connectivity of neural oscillations representing one of the key neural mechanisms underlying DOC. This review examines research progress on neural oscillations in DOC diagnosis and treatment from three perspectives: theoretical foundations, clinical applications, and existing limitations. Neural oscillations refer to the periodic, synchronous firing activity of neuronal populations under specific conditions. Distinct differences in spectral characteristics, phase synchronization, and responses to neuromodulation are observed across varying severities of DOC. Electroencephalography (EEG)-based neural oscillation analysis reveals information transmission and processing capabilities at different consciousness levels, thereby facilitating more accurate discrimination between DOC severities and enabling therapeutic awakening through neural oscillation modulation. Despite current challenges including insufficient mechanistic research and slow clinical translation, neural oscillations have demonstrated substantial potential in DOC diagnosis and treatment.

Keywords: Consciousness Disorders; Neural Oscillations; Electroencephalography; Review

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Literature Search Strategy

Literature was retrieved from PubMed, Cochrane Library, and Web of Science using English keywords including "neural oscillation," "electroencephalography," "consciousness disorder," "diagnosis," "treatment," "therapeutic," and "perspective." Chinese databases including CNKI, Wanfang Data, and SinoMed were searched using Chinese keywords "神经振荡," "脑电图," "意识障碍," "诊断," "治疗," and "展望." The search timeframe spanned from database inception to June 20, 2023. Inclusion criteria comprised published literature with priority given to high-quality journal articles. Exclusion criteria included studies with insufficient data, duplicate publications, or unavailable full text.

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1 Neural Oscillation Mechanisms in DOC

Consciousness emergence depends on complex brain network connectivity and information processing. Two predominant neural mechanism hypotheses are the disconnection theory and the information integration theory. The disconnection theory posits that consciousness requires functional interaction between different brain regions, particularly key systems such as the anterior-posterior cingulate and default mode network. The information integration theory emphasizes that consciousness formation necessitates rapid and effective information integration across brain regions. Both hypotheses have limitations; wakefulness requires not only functional connectivity of critical systems but also optimized rapid information flow and integration among these systems. Neural oscillations reflect and influence brain information transmission and integration through their frequency, phase, and amplitude parameters, with disruption of neural oscillation synchronization and connectivity leading to DOC.

Consciousness relies on feedback from deep-layer neurons to superficial-layer neurons. Animal experiments have demonstrated that neurons in the thalamus and deep cortical layers are highly sensitive to consciousness state changes, capable of driving and regulating neural oscillation patterns in superficial cortical neurons to form critical consciousness circuits. This provides a theoretical foundation for detecting consciousness loop injuries through technical analysis of superficial neural oscillations. Different degrees of brain injury produce distinct cortical neural oscillation patterns, and during consciousness recovery, a shift in EEG peak frequency from the band to the α band has been observed. This may result from recovery of inhibitory GABAergic signaling in specific (mesocortical) neural circuits, reflecting the transition from unconsciousness to wakefulness. Theoretically, detecting neural oscillation patterns and their changes can probe consciousness-related brain network functions, detect residual consciousness, assess potential for consciousness recovery, and promote awakening through technical modulation to reinduce high-frequency neural oscillations.

2.1.1 Spectral Characteristics

Research has identified correlations between power changes in specific EEG frequency bands (δ, , α, etc.) and DOC severity. For instance, compared with minimally conscious state (MCS) patients, unresponsive wakefulness syndrome (UWS) patients show increased δ power and decreased α power. However, recent studies have found significant δ activity in the EEG of conscious patients, creating a paradox with earlier research that considered high-amplitude δ oscillations as a marker of consciousness loss. Therefore, relying solely on single-band power for DOC severity assessment has limitations. Researchers have developed EEG analysis methods that integrate multi-band features to improve diagnostic accuracy. The ABCD neuronal recovery model, based on combined δ, , α, and β bands, displays contribution degrees of different frequency oscillations through power spectral peaks and has proven valuable in DOC assessment.

The ABCD model reflects thalamocortical integrity by detecting specific cortical neural oscillation patterns to determine consciousness levels, compensating for clinical behavioral assessments that may overlook covert consciousness. Type "A" shows power spectral peaks only in the δ range (0–4 Hz); Type "B" in the range (4–8 Hz); Type "C" in both and β ranges (13–24 Hz); and Type "D" in α (8–13 Hz) and β ranges. Theoretically, progression from Type "A" to "D" corresponds to completely disconnected, severely disconnected, moderately disconnected, and intact thalamocortical network systems, respectively, with the cerebral cortex gradually generating higher-frequency oscillations, indicating enhanced capacity for information integration and processing, and progressively higher consciousness levels. Recent years have validated the ABCD model's application value in patients with post-cardiac arrest coma, acute traumatic brain injury, and subarachnoid hemorrhage. Overall, spectral characteristics have demonstrated advantages for rapid DOC screening in early stages, but they cannot reliably reflect information flow changes between neural networks mediated by synchronization. Current research remains largely exploratory with small samples, unified assessment standards have not been established, and guidance for treatment is lacking. From a clinical translation perspective, multi-center large-sample validation and integration with other assessment indicators are needed to establish a unified evaluation system for maximal clinical utility.

2.1.2 Phase Synchronization

Neural oscillations reflect rhythmic patterns of regional brain electrical activity, while phase synchronization depicts precise temporal relationships between oscillations in different regions from a dynamic perspective, reflecting both anatomical connectivity conduction effects and functional collaboration mechanisms. Synchronization of neural oscillations plays a critical role in consciousness state maintenance and transition. Compared with spectral analysis, phase synchronization analysis can more directly reflect connectivity changes between brain regions, thereby indicating the degree of neural network damage in DOC patients. VS patients exhibit reduced phase synchronization between frontal and posterior parietal regions compared with normal individuals, whereas MCS patients retain some degree of synchronous activity. Additionally, studies focusing on acute DOC prognosis assessment have found that EEG signal synchronization can predict patient outcomes, with survivors showing stronger EEG signal synchronization than non-survivors.

The advantage of phase synchronization analysis lies in its ability to directly reflect functional coordination states between brain regions to determine patient consciousness levels and prognosis. However, phase synchronization calculations are complex, require high signal quality and stability, and interpretation of synchronization patterns remains unclear. Current studies have small sample sizes, and synchronization type selection and parameter design lack standardization.

2.2 Therapeutic Effects of Inducing High-Frequency Neural Oscillations in DOC

Non-invasive neuromodulation techniques such as transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) have garnered attention for inducing high-frequency neural oscillations to improve consciousness levels in DOC patients. These approaches are primarily based on the plasticity of neural oscillations and the "neural oscillation entrainment" principle, whereby internal neural oscillation activity gradually synchronizes with external rhythmic stimulation. Clinical studies have confirmed that tDCS and rTMS can improve consciousness levels and restore awareness in some DOC patients.

For example, Xie et al. applied 10 Hz high-frequency rTMS to the left dorsolateral prefrontal cortex (DLPFC) and observed significant increases in high-frequency neural oscillations such as α and β waves and decreases in low-frequency δ and waves. Fan et al. similarly applied 20 Hz high-frequency rTMS to the left DLPFC in DOC patients, observing increased high-frequency and decreased low-frequency neural oscillations, with some patients showing varying degrees of consciousness improvement. The mechanism may involve rTMS activating the left DLPFC, increasing whole-brain cortical activity through cortico-cortical and cortico-subcortical networks, repairing consciousness networks, and restoring neural oscillations. Thibaut et al. applied tDCS to DOC patients, observing significant increases in cortical γ waves, possibly through direct enhancement of high-frequency neural oscillation activity in cortical neurons by tDCS anodes, thereby improving consciousness levels and enhancing information processing and integration capabilities.

MCS patients show more significant therapeutic effects compared with UWS patients, which may help clinicians better differentiate consciousness states and serve as an important biomarker for distinguishing MCS from UWS. Recent years have seen exploratory studies on combined multimodal awakening approaches and parameter comparisons, providing insights for precise and individualized awakening therapy. However, current research paradigms for various neuromodulation techniques differ substantially, lacking unified fixed stimulation parameters, treatment durations, and stimulation sites, as well as large-sample multi-center studies. Determining appropriate parameters to reinduce high-frequency neural oscillations for individualized treatment represents an important research direction for DOC awakening, though this field remains in its infancy and requires more high-quality studies to validate the efficacy and feasibility of related methods.

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3 Limitations of Neural Oscillation Applications in DOC

Neural oscillation technology has demonstrated tremendous potential in DOC assessment and treatment, but several limitations persist in practical applications. Regarding assessment, EEG-based neural oscillation evaluation has limited spatial-temporal resolution, primarily restricted to cortical network assessment with insufficient detection of subcortical networks. Relying solely on spectral characteristics or phase synchronization has limited capacity for brain function assessment. New analytical techniques such as microstate analysis and artificial intelligence modeling are gradually demonstrating advantages in brain function evaluation, yet integrated brain function assessment models combining neural oscillation-related technologies with other modalities remain unestablished. The mechanisms of non-invasive neuromodulation are not fully elucidated; awakening therapy primarily focuses on chronic DOC, with limited evidence for acute DOC awakening studies. Therapeutic efficacy shows individual variation, mostly determined through behavioral assessment, with insufficient follow-up research on post-treatment neural oscillation pattern changes and their relationship with prognosis.

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4 Summary and Outlook

The process from neural oscillation generation to synchronization activity in distant regions plays a critical role in consciousness emergence and maintenance. Disrupted neural oscillation synchronization and connectivity represents one of the neural mechanisms of DOC, with different neural oscillation patterns observed across varying DOC severities. Assessment of brain function damage through spectral characteristics, phase synchronization indices, and responses to non-invasive neuromodulation can help more accurately differentiate DOC severities and facilitate better clinical decision-making. Inducing high-frequency neural oscillations based on neural oscillation entrainment principles and neural oscillation plasticity to achieve DOC neural network restoration and consciousness recovery represents an important future research direction for DOC awakening.

Author Contributions: ZHANG Huimin was responsible for conceptualization, literature collection, and manuscript drafting; SHAN Dawei contributed to literature collection; ZHANG Yan handled manuscript revision, quality control, and final approval, assuming overall responsibility for the article.

Conflict of Interest: The authors declare no conflicts of interest.

References

[1] GIACINO J T, KATZ D I, SCHIFF N D, et al. Practice guideline update recommendations summary: disorders of consciousness: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology; the American Congress of Rehabilitation Medicine and the National Institute on Disability, Independent Living, and Rehabilitation Research[J]. Neurology, 2018, 91(10): 450-460. DOI: 10.1212/WNL.0000000000005926.

[2] DOELLING K B, ASSANEO M F. Neural oscillations are a start toward understanding brain activity rather than the end[J]. PLoS Biol, 2021, 19(5): e3001234. DOI: 10.1371/journal.pbio.3001234.

[3] REDINBAUGH M J, PHILLIPS J M, KAMBI N A, et al. Thalamus modulates consciousness via layer-specific control of cortex[J]. Neuron, 2020, 106(5): 835-846. DOI: 10.1016/j.neuron.2020.01.005.

[4] MIERAU A, KLIMESCH W, LEFEBVRE J. State-dependent alpha peak frequency shifts: experimental evidence, potential mechanisms and functional implications[J]. Neuroscience, 2017, 360: 146-154. DOI: 10.1016/j.neuroscience.2017.07.037.

[5] ARNTS H, VAN ERP W S, BOON L I, et al. Awakening after a sleeping pill: restoring functional brain networks after severe brain injury[J]. Cortex, 2020, 132: 135-146. DOI: 10.1016/j.cortex.2020.08.011.

[6] PIARULLI A, BERGAMASCO M, THIBAUT A, et al. EEG ultradian rhythmicity differences in disorders of consciousness during wakefulness[J]. J Neurol, 2016, 263(9): 1746-1760. DOI: 10.1007/s00415-016-8196-y.

[7] FROHLICH J, TOKER D, MONTI M M. Consciousness among delta waves: a paradox?[J]. Brain, 2021, 144(8): 2257-2277. DOI: 10.1093/brain/awab095.

[8] MONTI M, SANNITA W. Brain function and responsiveness in disorders of consciousness[M]. Cham: Springer International Publishing AG, 2015.

[9] CURLEY W H, BODIEN Y G, ZHOU D W, et al. Electrophysiological correlates of thalamocortical function in acute severe traumatic brain injury[J]. Cortex, 2022, 152: 136-152. DOI: 10.1016/j.cortex.2022.04.007.

[10] SCHIFF N D. Mesocircuit mechanisms underlying recovery of consciousness following severe brain injuries: model and predictions[M]//MONTI M, SANNITA W. Brain Function and Responsiveness in Disorders of Consciousness. Cham: Springer, 2016: 195-204. DOI: 10.1007/978-3-319-21425-2_{15}.

[11] COMANDUCCI A, BOLY M, CLAASSEN J, et al. Clinical and advanced neurophysiology in the prognostic and diagnostic evaluation of disorders of consciousness: review of an IFCN-endorsed expert group[J]. Clin Neurophysiol, 2020, 131(11): 2736-2765. DOI: 10.1016/j.clinph.2020.07.015.

[12] FORGACS P B, ALLEN B B, WU X, et al. Corticothalamic connectivity in aneurysmal subarachnoid hemorrhage: relationship with disordered consciousness and clinical outcomes[J]. Neurocrit Care, 2022, 36(3): 760-771. DOI: 10.1007/s12028-021-01475-0.

[13] FORGACS P B, DEVINSKY O, SCHIFF N D. Independent functional outcomes after prolonged coma following cardiac arrest: a mechanistic hypothesis[J]. Ann Neurol, 2020, 87(4): 618-632. DOI: 10.1002/ana.25690.

[14] EDLOW B L, CLAASSEN J, SCHIFF N D, et al. Recovery from disorders of consciousness: mechanisms, prognosis and emerging therapies[J]. Nat Rev Neurol, 2021, 17(3): 135-156. DOI: 10.1038/s41582-020-00428-x.

[15] HUANG Z R, VLISIDES P E, TARNAL V C, et al. Brain imaging reveals covert consciousness during behavioral unresponsiveness induced by propofol[J].

Sci Rep, 2018, 8(1): 13195. DOI: 10.1038/s41598-018-31436-z.

[16] FORGACS P B, FREY H P, VELAZQUEZ A, et al. Dynamic regimes of neocortical activity linked to corticothalamic integrity correlate with outcomes in acute anoxic brain injury after cardiac arrest[J]. Ann Clin Transl Neurol, 2017, 4(2): 119-129. DOI: 10.1002/acn3.385.

[17] VALENCIA A L, FROESE T. What binds us? Inter-brain neural synchronization and its implications for theories of human consciousness[J]. Neurosci Conscious, 2020, 2020(1): niaa010. DOI: 10.1093/nc/niaa010.

[18] KING J R, SITT J D, FAUGERAS F, et al. Information sharing in the brain indexes consciousness in noncommunicative patients[J]. Curr Biol, 2013, 23(19): 1914-1919. DOI: 10.1016/j.cub.2013.07.075.

[19] ALNES S L, LUCIA M, ROSSETTI A O, et al. Complementary roles of neural synchrony and complexity for indexing consciousness and chances of surviving in acute coma[J]. Neuroimage, 2021, 245: 118638. DOI: 10.1016/j.neuroimage.2021.118638.

[20] BELIAEVA V, SAVVATEEV I, ZERBI V, et al. Toward integrative approaches to study the causal role of neural oscillations via transcranial electrical stimulation[J]. Nat Commun, 2021, 12(1): 2243. DOI: 10.1038/s41467-021-22468-7.

[21] ESTRANEO A, PASCARELLA A, MORETTA P, et al. Repeated transcranial direct current stimulation in prolonged disorders of consciousness: a double-blind cross-over study[J]. J Neurol Sci, 2017, 375: 464-470. DOI: 10.1016/j.jns.2017.02.036.

[22] FAN J Z, ZHONG Y H, WANG H J, et al. Repetitive transcranial magnetic stimulation improves consciousness in some patients with disorders of consciousness[J]. Clin Rehabil, 2022, 36(7): 916-925. DOI: 10.1177/02692155221089455.

[23] BAI Y, XIA X Y, LI X L, et al. Spinal cord stimulation modulates frontal delta and gamma in patients of minimally consciousness state[J]. Neuroscience, 2017, 346: 247-254. DOI: 10.1016/j.neuroscience.2017.01.036.

[24] XIA X Y, BAI Y, ZHOU Y Z, et al. Effects of 10 hz repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in disorders of consciousness[J]. Front Neurol, 2017, 8: 182. DOI: 10.3389/fneur.2017.00182.

[25] THIBAUT A, BRUNO M A, LEDOUX D, et al. tDCS in patients with disorders of consciousness: sham-controlled randomized double-blind study[J]. Neurology, 2014, 82(13): 1112-1118. DOI: 10.1212/WNL.0000000000000260.

[26] CAVINATO M, GENNA C, MANGANOTTI P, et al. Coherence and consciousness: study of Fronto-parietal gamma synchrony in patients with disorders of consciousness[J]. Brain Topogr, 2015, 28(4): 570-579. DOI: 10.1007/s10548-014-0383-5.

[27] XIONG Q, LE K, TANG Y L, et al. Effect of single and combined Median nerve stimulation and repetitive transcranial magnetic stimulation in patients with prolonged disorders of consciousness: a prospective, randomized, single-blinded, controlled trial[J]. Front Aging Neurosci, 2023, 15: 1112768. DOI: 10.3389/fnagi.2023.1112768.

[28] WANG J M, XU L, GE Q Q, et al. EEG microstate changes during hyperbaric oxygen therapy in patients with chronic disorders of consciousness[J]. Front Neurosci, 2023, 17: 1145065. DOI: 10.3389/fnins.2023.1145065.

[29] ZHANG G J, ZHOU Y B. Artificial intelligence and machine learning in clinical medicine[J]. N Engl J Med, 2023, 388(25): 2397-2398. DOI: 10.1056/NEJMc2305287.

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