*Review*

# Evaluation of Consciousness Rehabilitation via Neuroimaging Methods

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**Abstract:** Accurate evaluation of patients with disorders of consciousness (DoC) is crucial for personalized treatment. However, misdiagnosis remains a serious issue. Neuroimaging methods could observe the conscious activity in patients who have no evidence of consciousness in behavior, and provide objective and quantitative indexes to assist doctors in their diagnosis. In the review, we discussed the current research based on the evaluation of consciousness rehabilitation after DoC using EEG, fMRI, PET, and fNIRS, as well as the advantages and limitations of each method. Nowadays single-modal neuroimaging can no longer meet the researchers` demand. Considering both spatial and temporal resolution, recent studies have attempted to focus on the multi-modal method which can enhance the capability of neuroimaging methods in the evaluation of DoC. As neuroimaging devices become wireless, integrated, and portable, multi-modal neuroimaging methods will drive new advancements in brain science research.

**Keywords:** disorders of consciousness; EEG; fMRI; PET; fNIRS; multimodal

## 1. Introduction

Disorders of consciousness (DoC) generally refers to changes in arousal or awareness caused by severe brain injury [1]. DoC mainly includes coma, unresponsive wakefulness syndrome/vegetative state (UWS/VS) [2], and minimally conscious state (MCS). The consciousness state of most DoC patients is difficult to alter and will remain in a particular state for months or years, which places a considerable burden on families and society. Accurate evaluation of consciousness rehabilitation is crucial for personalized and precise treatment on DoC patients. Behavioral assessment scales are widely used in clinical settings and the coma recovery scale revised (CRS-R) has become the gold standard for evaluation the consciousness rehabilitation of DoC patients [3,4]. However, misdiagnosis remains a serious issue, a study [5] shows that approximately 40% of DoC patients are misdiagnosed as UWS due to their inability to communicate, since patients' level of consciousness could fluctuate due to the passage of time and influence of external stimuli. An increasing number of studies indicated that neuroimaging methods can show residual brain activity in patients who have no evidence of consciousness in behavioral or clinical assessments. These patients consciously regulate their brain activity in response to commands and even answer "yes" or "no" questions by performing mental imagery tasks [6, 7].

Neuroimaging methods for consciousness rehabilitation evaluation is divided into two categories: resting-state and task-based paradigms. The resting-state paradigm detects spontaneous brain activity in patients without any stimulation, while the task-based paradigm detects brain activity changes in response to external stimuli or by having patients perform specific tasks. Neuroimaging methods do not rely on subjective judgment and assist doctors with objective, quantifiable characteristics to evaluate patients' consciousness rehabilitation. Hopefully, neuroimaging methods will improve the survival rate of DoC patients.

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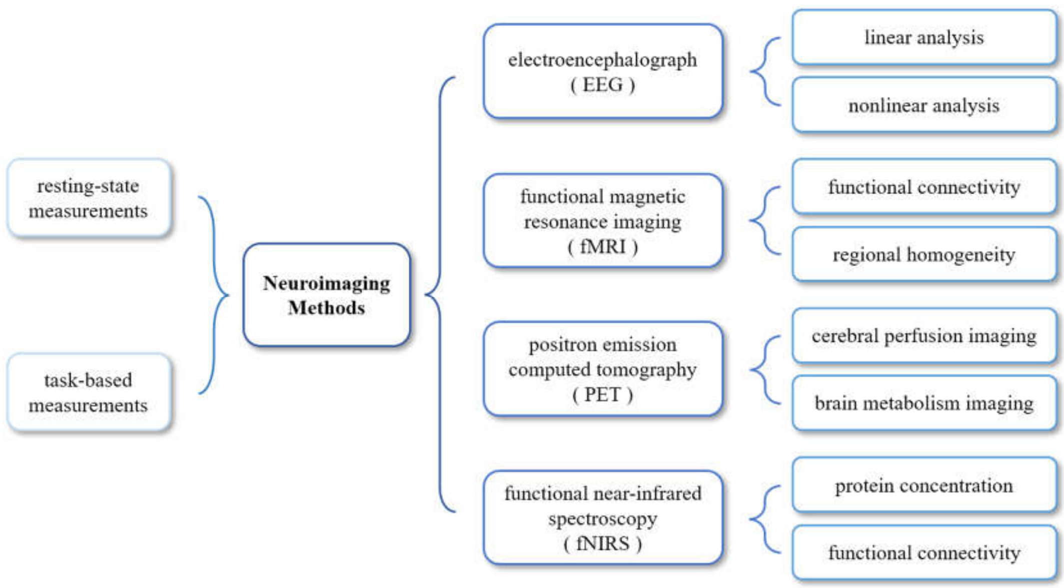


**Figure 1.** Various neuroimaging methods.

The paper reviews the application of neuroimaging methods in the evaluation of consciousness rehabilitation of DoC patients, including traditional electroencephalography (EEG), functional magnetic resonance imaging (fMRI), positron emission computed tomography (PET), and burgeoning functional near-infrared spectroscopy (fNIRS) (Figure 1). Neuroimaging studies in DoC patients are searched on ScienceDirect, Web of Science. And scientific conference documents, study protocols are excluded. The following keywords are used to search the appropriate studies for this literature review: (1) DoC; (2) neuroimaging; (3) EEG; (4) fMRI; (5) PET; (6) fNIRS; (7) multi-modal. The advantages and limitations of each method are discussed and the potential research directions are provided. Due to the inherent limitations of single techniques, an increasing number of studies are adopting multi-modal methods to evaluate consciousness rehabilitation in DoC patients. The review paper also discusses the potential and challenges faced by multi-modal neuroimaging methods, which offers new perspectives for the clinical assessment of DoC patients using neuroimaging methods.

## 2. EEG Used in DoC Studies

With the advantage of being economical and portable, EEG has been applied earlier in the evaluation of consciousness rehabilitation among various neuroimaging methods [8]. EEG studies in DoC patients can be mainly divided into two main methods: linear and nonlinear analysis [9]. The linear analysis reflects brain function by extracting information in the time or frequency domain of EEG signals, such as event-related potential (ERP), power spectral density (PSD), coherence, etc. Nonlinear dynamics features can represent the intensity of neuronal activity in brain waves and brain regions, which allows the brain to be viewed as a very complex chaotic system [10]. The nonlinear analysis uses analytical methods such as sample entropy (SampEn), fuzzy entropy (FE), permutation entropy (PE), Lempel-Ziv complexity (LZC), detrended fluctuation analysis (DFA), etc. (Figure 2)

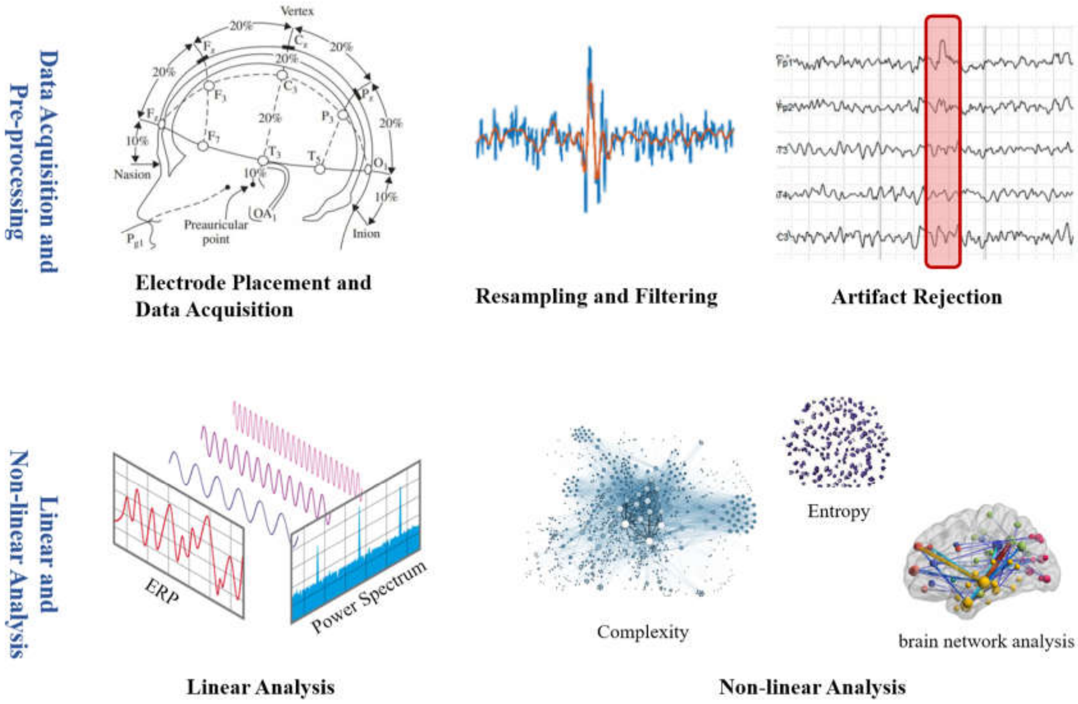


**Figure 2.** EEG acquisition and analysis.

Resting-state EEG detects the electrophysiological signals of the brain in DoC patients without any stimulation and acquires information about the spontaneous physiological activity of the brain. During the acquisition EEG in resting-state, the patient is usually asked to close his eyes and remain awake and relaxed [11]. Lehembre et al. found that EEG power spectrum of UWS patients increased in the delta band but decreased in the alpha band. And the connectivity (including features such as coherence and phase lag index) in theta and alpha bands was significantly lower in UWS patients than that in MCS patients [12]. Schorr et al. further investigated the differences in EEG coherence among different brain regions of DoC patients, which provides new theoretical support for EEG coherence as a potential marker of consciousness rehabilitation [11]. Dynamic functional connectivity (DFC) is commonly used in previous fMRI analysis, Naro et al. introduced DFC into the resting-state EEG study, and found that EEG-based DFC was significantly correlated with behavioral scale scores [13]. Stefan et al. applied multiple resting-state EEG analysis methods (entropy, PSD, coherence, complex network analysis, etc.) on the same dataset and combined multiple features by using a generalized linear model to classify UWS and MCS patients. The results showed that combining these features seemed to afford high prediction power and the value of AUC reached 92 ± 4% [14].

Early task-based EEG studies mostly applied event-related potentials (ERP) to evaluate the consciousness rehabilitation of DoC patients. ERP shows the potential changes induced in specific brain regions when the body receives stimuli associated with specific awareness or cognitive events. In 1990 O'Mahony et al. used EEG to evaluate comatose patients and found that auditory-related P300 potentials were associated with consciousness recovery [15]. Kempny et al. used DoC patients' names, others' names and reversed other names as ERP stimuli and detected statistically significant differences in patients' ERP latencies to their own names versus other people's names [16]. Wu et al. applied quantitative electroencephalography (QEEG) to monitor DoC patients' responses to music, their own names and noise. The study showed that brain activation of patients was highest when stimulated by their own names, and QEEG index in specific stimulation states may be an indicator of consciousness rehabilitation in DoC patients [17]. Li et al. found that patients' hobby stimuli evoked stronger changes in EEG characteristics compared to music stimuli, and the changes were more pronounced in MCS patients than UWS patients [18]. Sinitsyn et al. compared the perturbational complexity index (PCI) of DoC patients receiving TMS-EEG stimulation and found that high PCI value was related to well consciousness rehabilitation of DoC patients [19].

EEG records electrophysiological signals from the human scalp and has a higher temporal resolution compared to other metabolism-based techniques (fMRI, PET, fNIRS) [20]. However, EEG has a lower spatial resolution than other methods because it is susceptible to volume conduction effects [21]. Compared to fMRI, EEG allows minor movements and does not require special handling of patients, thus acquisition of EEG becomes more convenient [22]. EEG technology was applied earlier and therefore EEG-related analytical methods are well-established. It has been demonstrated that EEG correlates with the consciousness rehabilitation of DoC patients, and task-based EEG signals exhibit better performance in characterizing the state of consciousness and cognitive abilities of the brain [23]. Part of the studies [14, 24] have turned to fuse multiple EEG features to improve the evaluating ability of DoC patients, which requires a larger number of samples. TMS-EEG provides a new means for the diagnosis and assessment of DoC patients, and the study of TMS-EEG mapping would be a potential direction for the localization of awareness in DoC patients [25,26].

## 3. fMRI Used in DoC Studies

The fMRI rose in the 1990s and reflects the internal brain function based on the neurovascular coupling mechanism by detecting the blood oxygenation level dependent (BOLD) signal (Figure 3). Currently, it is primarily employed in investigating cognition and mental disorders [27].

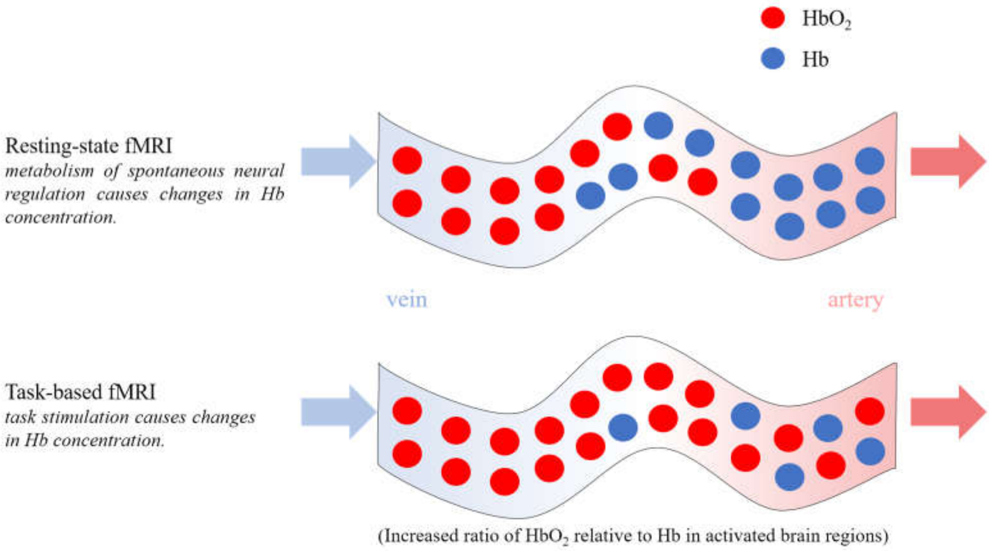


**Figure 3.** Principle of resting-state and task-based fMRI

Task-based fMRI studies using auditory stimuli have been widely applied in DoC patients, as they are easier to achieve. DI et al. analyzed the brain signals using fMRI when DoC patients hearing their own name called by a familiar voice (SON-FV), and the study found a significant activation in their brains [28]. Further studies have demonstrated that UWS/VS and MCS patients are capable of retaining brain responses to language and auditory stimuli, and fMRI is able to identify these responses [29]. Okumura et al. evaluated UWS/VS patients after music stimulation using fMRI and found that activation in bilateral temporal lobes was related to the recovery of consciousness [30]. Wang et al. found that the types and volumes of auditory cortex activation induced by SON-FV were significantly correlated with the prognosis of UWS/VS patients, which suggested that repetitive use of the simple fMRI task may provide more reliable prognostic information [31]. In a recent study, Boltzmann et al. scanned UWS/VS patients with scanner noise, preferred music and aversive auditory stimulation, and found that UWS/VS patients showed more significant responses to preferred music and aversive auditory stimulation, finally, the study indicated that UWS/VS patients require strong stimuli to elicit cerebral responses [32]. Researches based on active fMRI paradigms have also made some progress. Liang et al. considered four imagery tasks (imagine navigating home, imagine playing tennis, imagine familiar faces, mental counting and rest) and found that different tasks activated the brain differently [33]. Wang et al. found that the simple active fMRI “hand-raising” task can elicit brain activation in patients with DoC. Activity of the motor-related network may be taken as an indicator of high-level cognition that cannot be discerned through conventional behavioral assessment [34]. Clinical implementation of fMRI motor imagery paradigms for detection of consciousness will require further development, validation, and optimization of standardized approaches to fMRI data acquisition, analysis and interpretation [35].

Resting-state fMRI is a popular and advanced technique for studying the functional structure and static networks of the brain, because interaction with DoC patients and difficult experimental set-ups are not required [22]. Luppi et al. found that human consciousness relies on the spatiotemporal interactions between brain integration and functional diversity by comparing resting-state fMRI data of awake volunteers, propofol-anesthetized volunteers and DoC patients [36]. Early studies have shown that the resting-state functional connectivity within the default mode network is decreased and proportional to the degree of consciousness impairment, from locked-in syndrome to MCS, VS, and coma patients [37]. Huang et al. further analyzed resting-state fMRI signals of DoC patients and identified that human consciousness primarily depends on the default mode and the dorsal attention networks [38]. Qin et al. analyzed fMRI data of patients with varying degrees of consciousness impairment and demonstrated that the supplementary motor area, bilateral supramarginal gyrus (part of inferior parietal lobule), supragenual/dorsal anterior cingulate cortex, and left middle temporal gyrus play important roles in maintaining brain consciousness [39].

fMRI is a non-invasive neuroimaging technique with a high spatial resolution for accurate functional localization so it can effectively detect covert consciousness that cannot be demonstrated through clinical behavior. However, fMRI is susceptible to motion artifacts, thus has the limitations of low temporal resolution and high costs. Additionally, fMRI is not suitable for DoC patients in the Intensive Care Unit (ICU). Currently, fMRI has entered the era of "big data" with the establishment of large-scale brain datasets and the accumulation of research findings [40]. The quality of fMRI data plays a critical role in the accuracy and reproducibility of research. Li et al. proposed a new denoising method called linked independent component analysis, which helps improve the accuracy and reproducibility of fMRI studies [41]. In addition, traditional field strengths (1.5T and 3T) have reached their limits in terms of spatiotemporal resolution and signal-to-noise ratio balance. However, Ultrahigh magnetic field strengths (7T and above) allow functional imaging with even higher functional contrast-to-noise ratios for improved spatial resolution and specificity compared to traditional field strengths (1.5 T and 3 T), Which offers improved sensitivity and functional specificity for fMRI applications [42]. In the future, fMRI will focus on personalized applications, standard acquisition of data and fusion of different techniques.

**4. PET Used in DoC Studies**

PET, as a more established technique for studying consciousness, use different markers to measure glucose metabolism, oxygen consumption, focal cerebral blood flow and the distribution of specific neurotransmitters [43]. These markers can be used to assess the degree of residual brain function in patients with impaired consciousness [44].

PET includes two main imaging methods: cerebral perfusion imaging and cerebral metabolic imaging. Cerebral perfusion imaging employs imaging agents that are capable of traversing the blood-brain barrier and gaining entry into cerebral tissue where they exhibit stability and concentrate. Subsequently, cerebral perfusion images can be acquired by nuclear medicine imaging equipment. Patients with disorders of consciousness are severely ischemic in localized brain regions, and therefore cerebral perfusion imaging shows localized hypoperfusion or even no perfusion, which is manifested by low concentration or without concentration of the imaging agent.

Task-based DoC studies mostly use $H_2{}^{15}O$-based cerebral perfusion imaging methods which assist experts to further predict the possibility of recovery in DoC patients by evaluating the specific and directional responses produced by DoC patients under external stimuli. Under the stimuli of auditory, visual and nociceptive, a dissociation occurs between the low-level activation of the

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primary sensory cortex and the activation of higher cortical networks in DoC patients. [45-48]. Although task-based PET studies have yielded some results, there is still a demand for more extensive clinically responsive neuroimaging studies due to small number of studies and single cases, which make the task-based PET become a reliable tool for clinical assessment and treatment decisions in DoC patients.

In the studies of resting-state PET, brain metabolic imaging techniques are more widely used. Part of the study based on $\gamma$-aminobutyric acid receptor imaging agent observed the retention of injured brain neurons, while ligand $^{11}$C-labeled flumazenil ($^{11}$C-FMZ) was used to assess neuronal integrity and activity [49]. Rudolf et al. used $^{11}$C-FMZ to observe the local cerebral glucose metabolism of 9 VS patients caused by hypoxia and found that $^{11}$C-FMZ PET is important in the prognostic assessment of VS. More scholars have studied resting state DoC using $^{18}$F-labeled FDG-PET/CT [50]. As the main imaging agent for current PET/CT imaging, $^{18}$FDG can accurately reflect the glucose metabolism of organs or tissues in vivo. Zhao Jing et al. analyzed glucose metabolism in various brain regions of 40 VS patients, 12 MCS patients and 11 DoC patients with regained consciousness, and the results showed that standard uptake values in all brain regions except the brainstem were significantly different among the three groups of patients [51]. Usami et al. further found that functional preservation in the left occipital region in patients with chronic DoC might reflect an awareness of external environments, whereas extensive functional preservation in the right cerebral hemisphere might reflect communication motivation. [52]. Yamaki et al. investigated whether regional brain glucose metabolism assessed by $^{18}$F-FDG-PET in resting-state could predict voluntary movement in patients with DoC following severe traumatic brain injury. The research showed that glucose uptake in the left proximal and right proximal limb of the primary motor cortex may reflect contralateral voluntary movements [53]; Another study found a significant difference in glucose metabolism in the thalamus, brain stem, and cerebellum between comatose and noncomatose patients acutely after TBI. The metabolic rate of glucose in these regions significantly correlated with the level of consciousness at the time of PET. [54]. All these studies demonstrated the correlation between the rate of cerebral glucose metabolism and the level of consciousness.

Being sensitive to damaged brain cells, PET can accurately and objectively reflect the functional state of brain cells to assess the degree of brain cell damage. However, PET has a certain degree of radioactive damage, although the application of short-half-life radioisotopes could mitigate the adverse effects, it increases the imaging time and has a low spatial resolution, all these reasons greatly limit the application of PET/CT. In the future, taking into account both safety and accuracy, more suitable tracers will be explored to improve the effectiveness of PET in consciousness evaluation of DoC patients. Fusion with other methods is another potential direction for PET studies. PET is less sensitive to rapid and transient changes [55], whereas EEG records brain activity in the millisecond range. Therefore, the combination of both methods may obtain greater performance in the evaluation of DoC patients. In addition, Luppi et al. used a PET and MRI based dynamic mean field (DMF) model to explore the neurobiological mechanisms of consciousness loss in anesthesia and DoC patients [56]. The study provides a new idea for the evaluation of DoC recovery using PET/MRI (Figure 4).

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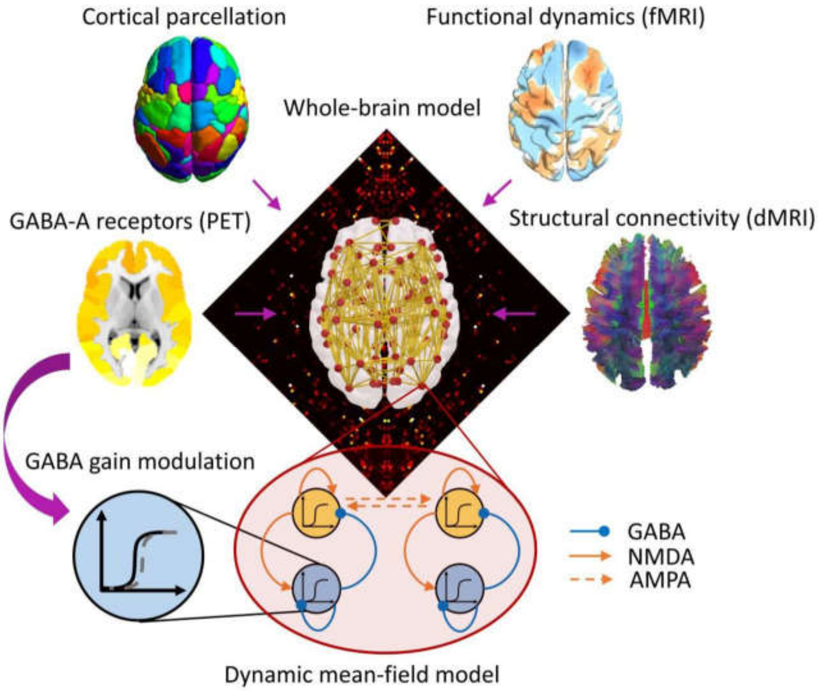


**Figure 4.** Multimodal study based on PET and MRI [56].

## 5. fNIRS Used in DoC Studies

fNIRS is a non-invasive optical technique based on the different absorption spectral properties of oxyhemoglobin ($HbO_2$) and deoxyhemoglobin (HbR) in human tissues. By calculating the concentration variation of both proteins, fNIRS can be used to evaluate the recovery from DoC and thus reflect the functional state of the brain [57].

There is still a relatively small amount of research based on resting-state fNIRS. Liu et al. acquired resting-state fNIRS from 23 DoC patients and found that MCS and UWS have different patterns of topological architecture and short- and long-distance connectivity in prefrontal cortex, which confirmed that fNIRS is remarkable in distinguishing MCS and UWS [58]. Shu et al. studied that resting-state fNIRS based functional connectivity analysis of brain networks can quantify brain communication efficiency, which would be a potential functional indicator for DoC rehabilitation [59].

Due to the portability, fNIRS devices were widely used for task-based studies [60]. fNIRS identifies patients with potential consciousness by detecting brain activity during command-driven tasks and assesses their residual awareness. Existing studies mainly use active paradigms (including motor imagery and mental arithmetic tasks). Kempny et al. evaluated the brain function of DoC patients by recording their fNIRS signals under motor imagery tasks [61]. Research has shown that MCS patients prefer to experience "typical" fNIRS responses, and their hemodynamic responses were similar to those of the control group. It confirmed the feasibility of using fNIRS to evaluate the brain function of pDoC patients through motor imagery tasks for the first time. Li et al. used fNIRS combined with an active motor imagery paradigm and demonstrated the feasibility of the paradigm to study the functional brain activity of MCS patients [62]. The study provided new method to objectively evaluate the consciousness and residual awareness in MCS patients. The mental arithmetic task, another fNIRS research paradigm which requires higher degree of active consciousness in subjects, has been conducted [63], however, the related studies is limited and the probability yielding positive results is relatively low, thus requiring an expanded sample study for further validation.

The fNIRS studies applying with passive paradigm have also achieved notable outcomes. Current researches focus on spinal cord stimulation (SCS). Si et al. found that when high frequencies of 70 Hz and 100 Hz were selected for SCS, patients showed significantly enhanced cerebral hemodynamic responses in the prefrontal region and stronger functional connectivity between the

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prefrontal and occipital lobes [64]. Zhang et al. found a significant increase in cerebral blood volume in the prefrontal cortex at an interstimulus interval of 30 s for SCS [65]. Part of the studies used non-traumatic stimuli. Bicciato et al. first used a frequency domain approach to investigate the variations in the oscillatory signal of fNIRS in the low frequency (LFO) and very low frequency oscillation (VLFO) spectral regions in patients with impaired consciousness under musical stimulation [66]. The study suggests that the use of fNIRS to identify typical patterns of brain responses to specific environmental stimulation may be a potential way to detect covert awareness in clinically unresponsive patients.

Compared with fMRI and PET, fNIRS has the advantages of higher temporal resolution, lower cost, and high portability, as well as being less susceptible to head movements and metal implants inside the body, thus facilitating follow-up measurements and clinical application. Compared with EEG, fNIRS possesses relatively high spatial resolution, resistance to motion interference and resistance to electromagnetic interference. Since fNIRS only detects in the cerebral cortex, it has weaker sensitivity towards the deep regions of the brain and therefore cannot detect information in the deeper part of the brain; moreover, the temporal and spatial characteristics make its signal processing and data analysis algorithms lack uniform standards.

In the future, fNIRS is expected to be fused with other neuroimaging methods to achieve multimodal neuro-detection for more accurate and comprehensive evaluation. In addition, the use of time-domain-based functional near-infrared spectroscopy (TD-fNIRS) and frequency-domain-based functional near-infrared spectroscopy (FD-fNIRS) can improve the sensitivity of fNIRS towards the deep brain (Figure 5). More sophisticated machine learning approaches such as artificial neural networks could also help improve the sensitivity of fNIRS [67]. Finally, researchers should establish a unified and effective method for fNIRS data analysis for the promotion and application of fNIRS.

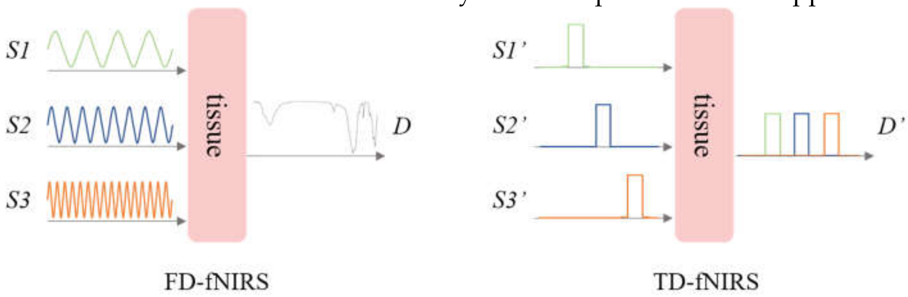


**Figure 5.** Frequency-domain and time-domain fNIRS.

## 6. Conclusions

Although there is still wide disagreement about what exactly consciousness is [68], neuroimaging methods have been proven to be effective in consciousness rehabilitation evaluation. Especially in patients without command following or other signs of consciousness at the bedside, neuroimaging methods are useful to detect covert consciousness (if present), avoid misdiagnosis [69] and help patients to communicate with the outside world [70]. PET can accurately and objectively reflect the functional status of brain cells. However, compared with other methods, it has a certain degree of radioactive damage, which limits the development of related studies. Considering both safety and accuracy, exploring tracers with greater performance is a potential research direction. Among lots of neuroimaging methods, EEG and fMRI are more widely used. EEG has made great progress in the evaluation and classification of DoC patients in task-based paradigms due to its high temporal resolution, whereas fMRI has a unique advantage in functional brain networks due to its high spatial resolution [71]. EEG has a lower spatial resolution than other methods because it is susceptible to volume conduction effects. High-density EEG paradigms appear to have a high specificity but very low sensitivity for the detection of covert consciousness [69]. fNIRS has a moderate spatial and temporal resolution, and has become a burgeoning tool for the evaluation of DoC because it is more portable and economical. Currently, single-modal neuroimaging cannot meet the requirements of researchers. Multi-modal methods can achieve complementary advantages of

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different methods and integrate both the temporal and spatial information of the brain. PET/MRI can evaluate brain structure and metabolism at the same time [56], helping doctors to increase the probability of detecting (spared) functional connectivity [72]. Simultaneous PET/MRI allows spatial and temporal correlation of the signals from both modalities, creating opportunities which are impossible to realize using sequentially acquired data [73]. The fusion application of fMRI and EEG can precisely locate brain activity in time and space due to the complementary nature of their spatiotemporal resolution [74]. Based on combined EEG and fMRI features, models which use machine-learning algorithms (SVM and Random Forest) predicted consciousness levels with improved positive predictive value and sensitivity [75]. However, the bulky size of fMRI equipment makes it difficult to collect data in ICU [76]. While maintaining portability, fNIRS can be collected simultaneously with EEG to improve its sensitivity, which makes multi-modal detection more convenient. fNIRS captures different correlates of brain activity than EEG: While fNIRS detects metabolic response to cognitive activity, EEG measures an electrical process which does not interfere with the light signals measured by fNIRS. The improved spatial resolution offered by fNIRS can provide information regarding the active source location, thus complementing EEG findings [77]. The application of multimodal neuroimaging methods requires substantial data, which increases the workload of researchers. As neuroimaging devices become wireless, integrated and portable, multi-modal neuroimaging method is expected to have a broader application in the evaluation of consciousness rehabilitation and will drive new advancements in brain science research.

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