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Original Research

The Evaluation Indexes Suitable for Nonhuman Primates can be Extracted from Clinical Consciousness Disorder Assessment Scales: A Hypothesis

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Abstract

Background: Currently, case studies or clinical trials in different patient populations remain the main resource underlying the understanding of disorder of consciousness (DoC). This provides a low efficacy for the derivation of data and the implementation of associated controlled experimental designs. Preclinical models provide precise controls, reduced variability, rich data output and limited ethical complexity. Nonhuman primates are suitable model animals for disorders of consciousness due to their brain structure being very similar to that of humans. Behavioral tests remain the primary standard for assessing the consciousness status of humans. However, there is currently no behavioral assessment scale available for evaluation of the state of consciousness disorder in nonhuman primates. This presents a significant challenge for the establishment of different models of consciousness disorder. Therefore, there is considerable motivation to focus on the development of a proper tool for assessment of the state of consciousness associated with nonhuman primate models that are based on clinically common consciousness assessment scales. **Methods**: It is assumed that the Delphi and level analysis methods based on clinical consciousness disorder assessment scales may provide an effective way to select and include assessment indexes for levels of consciousness in nonhuman primates. **Results**: 8 first-level indicators with 41 second-level indexes were selected preliminary as a pool of evaluation entries of state of consciousness of nonhuman primates. **Conclusions**: It may be practicable to extract appropriate indicators for non-human primates from the clinical consciousness disorder assessment scales. Besides, a combination of Delphi method, behavioral analysis, electroencephalography, neuroimaging (such as positron emission tomography-computed tomography) and functional magnetic resonance imaging is necessary to test the reliability and validity of the novel scale reported here.

Keywords: assessment scale; disorders of consciousness; nonhuman primates; animal models

1. Introduction

Consciousness is a very vague concept with no widely accepted definition. Generally, it can be divided into two aspects: (1) Content-related consciousness (i.e., the local state) and (2) The awakening state (i.e., the global state) [1–4]. Local states of consciousness include various perceptual experiences, for example, image, affect, body sensations and current thoughts. In the science of consciousness, local states are often referred to as contents of consciousness because they are usually distinguished from others by the objects and features they represent. However, global states of consciousness are not usually distinguished from one another based on the objects or features represented in experience. Rather, they are typically differentiated on the basis of cognitive, behavioral, and physiological factors [5]. The ability to stay awake and awareness of the environment are important characteristics of connection among conscious individuals [6].

Recently, with the rapid development of modern neuroscience and brain science, new technologies and strategies have been developed for the study of human and animal functions of consciousness. For this reason, the 2012 Cambridge Declaration on Consciousness was a turning point in the history of animal consciousness, stating in clear language that nonhuman animals have a similar state of consciousness to humans. Animals like humans, can sense, feel pain and have emotional responses [7]. Here, the main concern is the characteristics of consciousness in nonhuman primates. Ben-Haim *et al*. [8] used an elegant and simple visual counter-cuing task that found striking similarities between human and monkey behavior. The task required the subjects to shift their eyes from visual cues to reward goals. When the cue was displayed for 250 milliseconds, both subjects easily took their eyes off the cue. Conversely, when

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the cue was presented so briefly that the human reported not seeing it, neither human nor animal learned to look away and the behavior changed in the opposite direction. The cue captured attention, slightly increasing the amount of time the subjects looked at the reward location opposite the cue. Ben-Haim *et al*. [8] suggested that monkeys have both conscious and unconscious visual perception patterns based on the similarity between human and monkey eye movements. Conscious behavior suggests that nonhuman primate consciousness can be expressed as phenomenal consciousness. Being able to identify the self in a mirror is thought to be an effective means of verifying self-awareness. Chang *et al*. [9] found that trained rhesus monkeys spontaneously displayed the ability of mirror self-recognition through a new method of visual ontology position coupling training. Nonhuman primates do not have the ability to use language to express mental feelings. Some researchers have come up with ways to talk to them, with some remarkable results. Some researchers used hand gestures to communicate with them, while others simply spoke to them in American pantomime. The most interesting thing is to talk via the language of a keyboard, which has more than 200 keys, each printed with a different geometric pattern, one pattern representing a word or number. Chimps quickly learned to use this language system to communicate and express their needs [10]. This suggests that nonhuman primates are capable of perceiving external objects and associating with themselves, which is temporarily classified as access consciousness. Nonhuman primates show different awakening states in different brain injury states or different levels of anesthesia and they show different levels of loss of consciousness, as do humans. So, it is concluded feasible to use nonhuman primates as models for studying consciousness.

Nowadays, the survival rate of patients with severe brain injury and stroke has been greatly improved and there has been a large increase in the number of patients with clinical disorders of consciousness [11]. In the United States, approximately 100,000 to 300,000 people have been diagnosed with prolonged DoC, while in Europe the prevalence varies from 0.2 to 6.1 people per 100,000. There is no accurate data on prolonged DoC in China, but it is believed to have increased progressively there over time [12]. These people pose an extremely heavy burden on their families and society. For such reasons, there is strong motivation to seek improved treatments for consciousness disorders.

In clinical practice, recovery of consciousness (ROC) is rigorously assessed, including examination of cortical activity [13], spontaneous behavior and response to stimuli [14]. However, the detailed underlying mechanisms that support these changes remain unknown. Additionally, the lack of such information ultimately limits physicians in the accurate determination of levels of consciousness, which has a negative influence on making treatment plans to assess prognosis and estimated time to recovery from coma [15]. Currently, the understanding of DoC is largely dependent on individual case studies or clinical trials in different patient populations, which have limited ability to export data and implement controlled experimental designs [16]. It is predicted that preclinical models will provide precise control with reduced variability, rich data output and limited ethical complexity. Therefore, using animal models to elucidate unknown mechanisms appears to be the best choice. Rodents play a vital role in the study of disorders of consciousness, but they do not fully explain the mechanisms of disorders of consciousness and it is likely not possible to model certain types of DoCs (such as diffuse axonal injury) [17]. Nonhuman primates have a developmental pathway similar to that of humans in terms of anatomy, physiology, genetics, neurological function as well as their cognitive, emotional and social behavior [18]. Therefore, NHPs have a unique advantage in modeling DoCs.

Although objective techniques such as electroencephalography (EEG) [19], neuroimaging (e.g., positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) [20]) can be used to evaluate consciousness of substitutes. The American Academy of Neurology and the American Clinical Neurophysiology Society define quantitative EEG as: "…the mathematical processing of digitally recorded EEG in order to highlight specific waveform components, transform the EEG into a format or domain that elucidates relevant information, or associate numerical results with the EEG data for subsequent review or comparison" [21]. Spectral power analysis is a standard EEG method, increased low power (δ and θ) and decreased high power (α) in resting EEG are common spectral features in DoC patients [22]. Evoked potentials are "electrical manifestations of the brain's reception of and response to an external stimulus" [21]. Several EEG markers, such as somatosensory evoked potential (SEP), auditory evoked potential (AEP) and event-related potential (ERP), are used in clinical routine and can be used to evaluate the prognosis of patients with DoC [23]. Functional imaging is able to detect local activity in different brain regions and explore their interactions. Resting-state fMRI and PET-CT analyses of whole-brain multiple network activation and connectivity strength add information to assessment and prognosis [24], however, fMRI and PET-CT studies easily produce motion artifacts, and patients with consciousness disorders have difficulty not moving limb parts, which causes problems with the evaluation of consciousness. Also, MR scanners are uncomfortable for patients with DoC. As a result, because these techniques are expensive, time-consuming and inconvenient to operate, behavioral test remains the best method for assessing human consciousness [25].

Robust operationally defined behavioral markers have been developed to distinguish conscious behaviors in clinical evaluation, particularly those scales that discriminate coma from related disorders of consciousness [26,27]. However, progress in the assessment of levels of consciousness in nonhuman primates is surprisingly limited compared to the quantitative behavioral assessments used for patient evaluations [28]. When Gennarelli *et al*. [29] constructed a diffuse axonal injury model of nonhuman primates, they found it difficult to describe the severity of coma. Systems describing human comas are not satisfactory for laboratory animals. For example, the Glasgow Coma Scale cannot be used because it relies on language elements and the assessment of response to motor commands. So a behavioral scale was developed to describe the severity of the coma. Loss of consciousness (LoC) may occur in sleep anesthesia and pathological states. The reconstruction of brain function after consciousness interruption is similar to the recovery of simulated pathological states, so there is positive clinical significance in its study. It is difficult to study the mechanism of the process of recovery of consciousness in both the unpredictability of the recovery of pathological state and the rapidity of the recovery of sleep. General anesthesia is a controllable and repeatable intervention, so the recovery process can be systematically studied by influencing consciousness under anesthesia. Tassie *et al*. [30] and Redinbaugh *et al*. [31] have developed evaluation indexes for the anesthetic awakening behavior of nonhuman primates which are based on clinical assessment scales for evaluation of the level of consciousness in nonhuman primates. However, this must be studied further if such evaluation indexes are to have credibility. Alternatively, there is currently no assessment method to test the level of consciousness in nonhuman primate models, which means it is a significant challenge to establish animal models at different levels of consciousness. Therefore, it is necessary to develop a behavioral scale for the evaluation of consciousness disorders in nonhuman primates. Having objective indicators will also allow meaningful comparisons across studies and optimize preclinical results which, as a consequence, are more likely to be successfully translated from the laboratory to the clinic. This will eventually improve the testing of treatments and help in the accurate diagnosis of disorders of consciousness and brain damage. It also helps to elucidate the detailed underlying mechanisms behind the clinical consciousness assessment of behavior scale.

2. Hypothesis

Nonhuman primates are very similar to humans in terms of genetic, neuroanatomical, cognitive and behavioral characteristics [18]. The authors' efforts are focused on the development of a suitable tool for assessing levels of consciousness in nonhuman primate models based on a clinically typically consciousness assessment scale.

3. Evaluation of the Hypothesis

The aim is to form a behavioral scale to evaluate levels of consciousness in nonhuman primates, in the expectation that it will assist in progression of verification of the foregoing hypothesis. Meanwhile, it is proposed that the Delphi technique and level analysis method may be used as an effective way to select and include assessment indexes for the level of consciousness in nonhuman primates. Finally, for nonhuman primate model animals with disorders of consciousness, it is proposed that a combination of behavioral analysis and fMRI, EEG and PET-CT will suitably test the reliability and validity the of scale developed.

3.1 Establishment of Evaluation Indexes

The Delphi technique [32] is a research method that aims to achieve a consensus judgment of experts. The consultation of such experts facilitates the development and prioritization of areas that can lead to actions for the resolution of social issues. The technique is widely used across many specialist professions working in social contexts [33] and is one comprised of five essential stages [34]:

(1) Constitution of an Expert Group;
(2) Establishment of a Pool of Evaluation Entries;
(3) Develop Expert Correspondence Questionnaire;
(4) Expert Selection and Consultation;
(5) Statistics Analysis.

The objective is to determine the consensus of expert opinion and reach consensus on the topic being studied. This is a very useful technique for pooling expert opinion on a topic to support innovative thinking or change in areas including health and rehabilitation [35]. The process could take two to four rounds, depending on the number of responses and the level of consensus. In the Delphi study, consensus was defined as greater than 70% agreement on all items with the same ranking [36].

3.1.1 Constitution of an Expert Group

An expert group should include professors major in neurobiology, neurology, neurosurgery, rehabilitation medicine, anesthesiology and veterinary medicine. The functions of an expert group are as follows: literature reviewing, preparation of expert letter consultation item pool, selection of expert letter consultation questionnaire, distribution and recycling, analysis and discussion of expert opinions, as well as the establishment of a nonhuman primate consciousness disorder evaluation index system.

3.1.2 Establishment of a Pool of Evaluation Entries

(1) Literature Search

By use of the resources of the Nanchang University Library, the following databases were selected: PubMed, Web of Science, Elsevier Science Direct, China National Knowledge Infrastructure (CNKI), Wanfang Data, China Science and Technology Journal Database (VIP) and the Chinese biomedical database (CBM). A literature search identified articles published as of 1 March 2022. A comprehensive literature search on consciousness assessment tools for nonhuman primates and humans was conducted, as well as similar studies in rodents, dogs, horses and other animals were searched.

Table 1. List of clinical consciousness disorders assessment scales based on literature search.

No.	Scale	Evaluation index
1	Rancho Los Amigos Level of Cognitive Functioning	Responsiveness (I–X)
2	Glasgow Coma Scale	Eye, verbal, motor
3	Edinburgh-2 Coma Scale	Pain, cognition
4	Comprehensive Level of Consciousness Scale	Eye responses, motor, posture, communication, general responsiveness
5	Glasgow-Liege Scale	Eye, verbal, motor, brainstem reflexes
6	Western Neuro Sensory Stimulation Profile	Visual, tactile, olfactory, arousal/attention, expressive communication, auditory, vocalization
7	Innsbruck Coma Scale	Eye responses, auditory, pain, posture, oral
8	Coma Near Coma Scale	Visual, auditory, command following, threat response, olfactory, tactile, pain, vocalization
9	Sensory Stimulation Assessment Measure	Auditory, vision, tactile, olfactory, gustatory, eye-opening, motor, vocalization
10	Chinese Vegetative State Scale	Motor, eye response, eating, emotional responses, command following, verbal
11	Coma Exit Chart	Facial expression, sensory functions: vision, auditory, tactile, motor abilities: eye-opening, head control, arm and hand control, leg control, vocalization
12	The Maryland Psychiatric Research Center Involuntary Movement Scale	Motor
13	Preliminary Neuropsychological Battery	Verification tasks
14	Sensory Modality Assessment Rehabilitation Technique	Auditory, vision, tactile, olfactory, gustatory, wakefulness, motor, communication
15	Wessex Head Injury Matrix	Basic behaviors, social/communication, attention/ cognitive, orientation/ memory
16	Neurobehavioral Cognitive Status Examination	Level of consciousness, orientation, attention, language, constructional praxis, memory, calculations, reasoning
17	Putney Auditory Comprehension Screening Test	Auditory comprehension screening test
18	Loewenstein Communication Scale	Mobility, respiration, visual, auditory, communication
19	Coma Recovery Scale-Revised Scale	Auditory, visual, motor, oral, communication, arousal
20	Full Outline of Un-responsiveness	Eye response, motor response, respiration, brainstem reflexes
21	Disorders of Consciousness Scale	Auditory, visual, tactile, sensory, swallowing, olfactory
22	Nociception Coma Scale-Revised	Motor response, verbal response, facial expression
23	Chinese Vegetative State Scale	Motor, eye response, auditory function, eating, emotional response
24	Adelaide Paediatric Coma Scale	Eye, verbal, motor
25	Steward Awakening Score	Consciousness, respiratory tract, physical activity
26	Modified Aldrete Recovery Score	Activity, respiratory, circulation, consciousness, O_2 saturation, pain
27	Glasgow-Pittsburgh score	Eye, verbal, motor, pupil, cranial nerve reflexes, seizures, spontaneous breathing

Thirteen primary search terms were used to define DoC: apallic syndrome, akinetic mutism, coma AND post-head injury, coma AND vegetative state, coma AND post-traumatic, coma AND post-trauma, minimally conscious, coma AND traumatic, persistent vegetative state, minimally responsive, prolonged post-traumatic unawareness, post-head injury coma and unawareness state. Each of the 13 primary terms was paired with 30 secondary terms that defined aspects of measurement: classification, assessment, course, diagnosis, evaluation, diagnostic, injury severity score, measure, instrument, natural history, observer variation, neurologic examination, outcome, predictive, prognostic, prognosis, progression, questionnaire, psychometric, recovery, reliability, scale, reproducibility of results, sensitivity, specificity, tool, test, trauma severity indices, validity and validation. Filter terms (e.g., animal, plant, ethics, religion) were used to eliminate irrelevant articles. Additional searches were conducted using scale names, abbreviations and author names. Finally, task force members used personal knowledge of DoC scale articles and examined references in reviewed articles to identify additional relevant articles. Finally, 27 scales were screened out, as shown in Table 1.

(2) Extract Evaluation Indexes

To better screen evaluation indicators the 27 behavioral scales for clinical evaluation of patient consciousness

Table 2. **Classification of evaluation indexes.**

First-level indexes	Second-level indexes	The number in Table 1
Sensory	Visual	6, 8, 11, 14, 15, 18, 19, 21
	Auditory	6, 7, 8, 11, 14, 17, 18, 19, 21, 23
	Tactile	8, 11, 14, 21
	Olfactory	8, 14, 21
	Gustatory	14, 21
	Vestibular sensation	21
	Pain	3, 7, 8, 26
Motor	Eye	2, 4, 5, 7, 9, 10, 11, 20, 23, 24, 27
	Oral/EatingSwallowing	10, 19, 21, 23
	Limbs	2, 4, 5, 9, 10, 11, 12, 14, 19, 20, 22, 23, 24, 25, 26, 27
	Posture	4, 7
	Face	11, 22
	Head	11
	Arms/Hands	11
	Leg	11
Verbal	Vocalization	9,11
	Verbal	2, 5, 7, 8, 10,16, 18, 19, 22, 24, 27
	Communication	4, 6, 14, 15, 19
	Social	1, 15
Perceptual	Perceptual	3, 13, 15, 16, 17, 21
	Emotional response	10, 23
	Command following	8,10
	Constructional praxis	16, 21
	Functional object application	6, 21
Brainstem reflexes	Pupil reflex	6, 7, 21, 22, 27
	Corneal reflex	20, 27
	Cough reflex	20
	Fronto-orbicular reflex	5
	Vertical oculocephalic reflex.	5, 27
	Horizontal oculocephalic reflex	5
	Oculo-cardiac reflex	5
	Blink reflex	18
Vital sign	Respiration	5, 18, 20, 21, 23, 26, 27
	Heart rate	21, 23
	Muscular tension	12
	Pupillary size	7, 21
	Circulation	23, 26
	O_2 Saturation	26
	Nausea/vomiting	26
	Sleep-wake cycle	23
Arousal		6, 14, 19, 25
Facial expression		11, 22
Attention		6, 15
Mobility		18
Threat response		8
Seizures		27

given in Table 1 were employed, including the grading standards of evaluation indicators and the operation process of evaluation indicators. Indicators were further classified and summarized in each scale from the dimensions of the evaluation indicators with the most frequently used one selected to help find the commonalities of these scales. These high frequency indicators will likely also be applied to the assessment of consciousness in nonhuman primates. Generally, first and second-level indicators were extracted and classified into 27 scales and the scale to which each indicator belonged was marked according to the number in Table 1, as shown in Table 2.

(3) Selected Evaluation Indexes

To obtain the comprehensive evaluation index system developed here a large number of articles about the physiological characteristics of nonhuman primates and the anesthesia awakening behavior of nonhuman primates were read. The appropriate indicators for evaluating the consciousness level of the model animal were then selected from the indicators in Table 2. Finally, 8 preliminary first-level indicators and 41 second-level indexes were selected (as shown in Table 3).

3.1.3 Develop Expert Correspondence Questionnaire

To obtain expert opinions on the preliminary evaluation indicators, an expert correspondence questionnaire was developed. The expert correspondence questionnaire consisted of three parts:

(1) Letter to experts: Including background of the study, purpose, methodology, questionnaire completion, timing and contact information.

(2) Evaluation index judgment table at all levels: including index item index importance score and modification suggestions. A Likert five level scoring method was used to evaluate the importance of indicators and 1–5 points were counted from completely unimportant to very important. Experts assigned the degree of importance of indicators at all levels and put forward suggestions for modification, deletion, or addition.

(3) Basic information about experts was obtained, including age, education, professional title and other general information, as well as familiarity with the survey content and the judgment basis of the self-evaluation table.

3.1.4 Expert Selection and Consultation

According to the purpose of the study, experts who are familiar with the operation process of the clinical consciousness level behavior assessment scale or intimately familiar with research into the neuroscience of nonhuman primates were selected. Specific selection criteria were as follows:

(1) Experts had a deputy senior professional title or above.

(2) More than 10 years of clinical practice in consciousness disorders or research in nonhuman primate neuroscience.

(3) Bachelor degree or above.

(4) Willing to answer the expert consultation questionnaire in every rounds.

Questionnaires were emailed to experts and they were told to return them within two weeks. If the questionnaire was not clear or items were missing, they were asked to please confirm by phone. After the first round of questionnaires collected, statistical analysis was conducted on index scores, expert opinions were collated, the discussion was organized among research group members according to index screening standards and expert opinions and indicators

Table 3. A Pool of Evaluation Entries of State of Consciousness of Nonhuman Primates.

Items	Score
Auditory	
Localization to Sound	2
Auditory Startle	1
None	0
Visual	
Normal	5
Object localization: Reaching	4
Visual Pursuit	3
Fixation	2
Visual Startle	1
None	0
Eye-opening	
Spontaneous eye-opening	3
Eyes open to speech	2
Eyes open to pain	1
No response	0
Motor	
Normal	6
Automatic Motor Response	5
Localization to Noxious Stimulation	4
Flexion/withdrawal to pain	3
Abnormal flexion to pain	2
Extension to pain	1
None	0
Orofacial movements	
Normal	4
Vocalize	3
Moan	2
Oral Reflexive Movement	1
None	0
Pupil response	
Normal	4
Sluggish	3
Unequal response	2
Unequal size	1
None	0
Brainstem reflexes	
All present	4
Lash absent	3
Corneal absent	2
Doll's eye/calorics absent	1
Carinal (all) absent	0
Breathing	
Normal	4
Periodic	3
Central hyperventilation	2
Irregular hypoventilation	1
None (apnea)	0

then were adjusted; The evaluation results of the first round were fed back when the second round of questionnaires was issued. After two rounds of letter consultation, expert opinion on the evaluation of each indicator tended to be consistent and letter consultation was stopped and finally, the evaluation index system of nonhuman primate consciousness disorder was formed.

3.1.5 Statistical Analysis

The results of the questionnaire were checked and entered in Excel 2021(Microsoft Corp., Redmond, WA, USA) and SPSS 21.0 (IBM Corp., Chicago, IL, USA) by two researchers. The count data were described by frequency and percentage and the measurement data expressed by mean and standard deviation. The positive coefficient of experts is expressed by the recovery rate of the questionnaire and the concentration of expert opinion is expressed by the mean of importance value, standard deviation and full score rate. The authority coefficient (represented by Cr) was expressed by the arithmetic mean of the judgment coefficient (Ca) and the familiarity coefficient (Cs) and the calculation formula was Cr = (Ca + Cs)/2. The degree of coordination of expert opinions was expressed by the coefficient of variation (CV) and Kendall's coefficient of concordance (Kendall's W). The CV reflects the degree of dispersion of expert opinion, Kendall's W valuates the degree of coordination among experts on the evaluation object. Its value is between 0 and 1 and the higher the value, representing the consistency of expert opinion, the better.

3.2 Validation of Evaluation Indexes

Additionally, to the clinical behavior assessment scale, which can be used to describe the level of consciousness of patients, the level of consciousness can also be assessed by objective techniques beyond consciousness. Currently recognized useful technologies are: EEG and neuroimaging (such as PET and fMRI). Bareham CA [37] used canonical correlation analysis to relate clinical (including CRS-R scores combined with demographic variables) and EEG variables to each other. This analysis revealed that the patient's age, and the EEG theta band power and alpha band connectivity, all of those contributed most significantly to the relationship between EEG and clinical variables. Moreover, they found that EEG measures recorded at the time of assessment augmented clinical measures in predicting CRS-R scores at the next assessment. The bedside EEG assessments conducted at specialist nursing homes are certified to be feasible, and it has clinical utility and complete clinical knowledge and systematic behavioural assessments to inform prognosis and care. Stender J [38] did repeated standardised clinical assessments with the Coma Recovery Scale-Revised (CRS-R), cerebral (18)F-fluorodeoxy glucose (FDG) PET, and fMRI during mental activation tasks. The results suggest that cerebral (18)F-FDG PET could be used to complement bedside examinations and predict long-term recovery of patients with unresponsive wakefulness syndrome. Active fMRI could be useful for differential diagnosis. Both Ishizawa *et al*. [39] and Ballesteros *et al*. [40] used EEG to record neuronal dynamics in nonhuman primates during anesthesia induction from consciousness to loss of consciousness in real time, the latter also recorded the EEG signals during the recovery of consciousness in real time and the results showed that specific changes in EEG signals occurred during the recovery. Tasserie *et al*. [30] applied anesthesia to suppress consciousness in nonhuman primates. They found that during anesthesia, central thalamic stimulation induced arousal in an on-off manner and increased functional magnetic resonance imaging activity in prefrontal, parietal and cingulate cortices. These studies suggest that changes in the state of consciousness in nonhuman primates can be assessed using EEG and fMRI.

In the verification stage, consciousness will be assessed by the behavior assessment scale developed for the nonhuman primate model of consciousness disorder and animal behavior analysis software (such as DeepLabCut [41]). Other animal behavior analysis tools will be used to quantify behavior to verify each indicator. Meanwhile, objective techniques such as EEG and neuroimaging (such as PET and fMRI) will be applied to evaluate the level of consciousness in nonhuman primate animals models, compared with the results of the developed behavior assessment scale. Based on these information, the reliability and validity of scale and other measurement indicators can be tested. Additionally, some are clinically using extensive assessment scales or previously developed nonhuman primate consciousness assessment tools can also be used to assess the level of consciousness of nonhuman primates and observe which indices are related to EEG /fMRI/PET. Finally, results were compared with the Delphi method to verify whether the developed scale was meaningful for nonhuman primate consciousness assessment.

4. Conclusions

Loss of consciousness is a good model to study consciousness, including sleeping, anesthesia, coma and other disorders of consciousness. Currently, there are few studies on the assessment of consciousness in nonhuman primates. Tasserie [30] and Redinbaugh [31] proposed to evaluate the consciousness level of nonhuman primates in the process of anesthesia awakening based on clinical scales, but their evaluation method has not been confirmed to be accurate. Here, the interest is in loss of consciousness caused by disorders of consciousness such as coma. Although the hypothesis given above is also compiled based on clinical scales, the evaluation indicators proposed can be systematically verified by the Delphi method and associated objective techniques. A successful development of a behavioral scale for assessing the level of consciousness in nonhuman primates would be widely accepted in neuroscience. Meanwhile, it could overcome the difficulty of identifying the level of consciousness in the process of consciousness modeling of nonhuman primates and provide a valuable development to the field of consciousness and consciousness disorders.

5. Limitation and Outlook

The hypothesis described here is that nonhuman primate consciousness assessment scales can be constructed through literature review and Delphi method, with the main process being to extract indicators suitable for nonhuman primate consciousness assessment from existing consciousness assessment tools. Of course, it is not sufficient to construct a nonhuman primate consciousness scale by only a literature review, the selection of some indicators and evaluation of the importance of each indicator by experts. However, if behavioral changes of nonhuman primates can be observed in the process of consciousness recovery in combination with specific experiments, so as to explore the corresponding behavioral characteristics of different states of consciousness, a qualitative leap to the consciousness assessment scale constructed by Delphi method may be achieved.

Currently, it is difficult to construct a universally accepted scale for assessing the level of consciousness of nonhuman primates. Nonhuman primates are so valuable that studies are often limited by small sample sizes. And under the impact of the epidemic, it is difficult to carry out this work. So we want to use this hypothesis to call on a group of researchers who are interested in this research to do this work together. If a scientifically operable scale for assessing consciousness in nonhuman primates can be successfully developed, it may come into wide use and remove a further barrier to consciousness research.

Abbreviations

DoC, disorders of consciousness; RoC, recovery of consciousness; EEG, electroencephalography; PET, positron emission tomography; fMRI, functional magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography; SEP, somatosensory evoked potential; AEP, auditory evoked potentials; ERP, event-related potential; LoC, Loss of consciousness.

Author Contributions

WMS and CLM designed the study. CL performed the part research of nonhuman primates. XLD and CHL performed the part research of rehabilitation medicine. WMS and GXL wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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