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The visual stimulation in disorders of consciousness

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ABSTRACT

Severe brain damage usually leads to disorders of consciousness (DOC), which include coma, unresponsive wakefulness syndrome (UWS) and a minimally conscious state (MCS). Visual stimulation is widely used, especially in the diagnosis and treatment and treatment of DOC. Researchers have indicated that tests based on visual stimulation including visual pursuit, when used in conjunction with the Coma Recovery Scale-Revised, are able to differentiate between UWS from an MCS. Recently, targeting patients' circadian rhythms has been proposed to be a possible treatment target for DOC. Indeed, light therapy has been applied in some other fields, including treating seasonal affective disorder, sleep problems, and Parkinson's disease. However, at present, although visual stimulation and light therapy are frequently used in DOC, there is still no international unified standard. Therefore, we recommend the development of an international consensus in regard to the definitions, operational criteria and assessment procedures of visual stimulation and light therapy. This review combines visual stimulation, circadian rhythm recovery, and light therapy in DOC patients and presents the mechanisms and current advances in applications related to light therapy and visual stimulation in an attempt to provide additional ideas for future research and treatment of DOC.

KEYWORDS

Disorders of consciousness; visual stimulation; light therapy; patients' circadian rhythms

Introduction

Disorders of consciousness (DOC) are caused by severe brain damage (Luce, 2013) and included a set of altered states of consciousness. The two most important chronic forms are unresponsive wakefulness syndrome (UWS, which was previously referred to as a "vegetative state") and a minimally conscious state (MCS) (Bruno et al., 2011). UWS patients show only arousal but no awareness while MCS patients tend to show fluctuating but reproducible signs of consciousness (Giacino et al., 2018).

Because the mechanisms of consciousness generation have not yet been elucidated, the assessment of the level of consciousness in patients with DOC is currently carried out using behavioral and imaging methods. The assessment via patient's behavioral presentation is the easiest to perform at the bedside by providing simple multifaceted stimuli or commands and observing the patient's behavior. To date, various scales and scoring systems have been developed, such as the Glasgow coma scale, the disorders of consciousness scale, or the Coma Recovery Scale-Revised (CRS-R) (Bodart et al., 2013; Giacino et al., 2004; Reith et al., 2016). Among the visual-related assessment items, visual pursuit (VP) and visual fixation (VF) have been identified as the

first signs of consciousness emergence in individuals with DOC (Giacino et al., 2002; Overbeek et al., 2022). Many studies have also shown the importance of the visual cortex (striate cortex and extrastriate cortex) in the emergence of consciousness (Song et al., 2018).

Visual stimulation-based tests play an important role in the diagnosis of patients with DOC. At the same time, there are more visual stimulation-based interventions that have been used in the treatment of patients with DOC (the relevant studies in Table 1). Assessing and intervening at the level of consciousness is difficult in patients with DOC, as most of them have difficulty with movement and expression. There is no overview of the use of visual stimulation in patients with DOC as a tool that is easy to implement and has the potential to restore consciousness. Therefore, the present report focuses on this aspect.

Visual stimulation in diagnosis

Visual assessments are crucial for DOC patients as visual functions play an important role in the generation of consciousness.

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Table 1. Studies related to interventions using visual stimulation in patients with DOC.

	Sample	Methods	Result
Cheng et al.	<i>N</i> = 29 (48 ± 19 years old; 15 traumatic; 21 > a year post-injury; 11 VS and 18 MCS)	Withdrawal design (ABAB): During B phases, patients underwent a SSP (3 days a week, including auditory, visual, tactile, olfactory, and gustatory stimulation). Collect fMRI data.	Higher CRS-R total scores (medium effect size), higher arousal and oromotor subscores were observed in the B phases (treatment) in the MCS group but not in the VS group.
Arnaldi et al.	<i>N</i> = 27 (3.5 ± 2 months after brain injury)	Polysomnographic recordings were evaluated using visual and quantitative indexes.	The presence of sleep integrity (<i>p</i> = 0.0006), a better baseline clinical status (<i>p</i> = 0.014), younger age (<i>p</i> = 0.031).
Laura et al.	<i>N</i> = 91, 105 (the UK Biobank cohort)	Wrist-worn accelerometry data from participants were used to derive a circadian relative amplitude variable. Crosssectional associations between low relative amplitude and mood disorder, wellbeing and cognitive variables were examined in a series of regression models.	A quintile reduction in relative amplitude was associated with increased risk of lifetime major depressive disorder (MDD) (odds ratio (OR) = 1.06, 95% CI 1.04, 1.08) and lifetime bipolar disorder (OR = 1.11, 95% CI 1.03, 1.20).
Christine et al.	<i>N</i> = 18	A cross-sectional study: investigate the presence of circadian temperature rhythms across 6 to 7 days using external skin temperature sensors	Analyses with Lomb-Scargle periodograms revealed significant circadian rhythmicity in all patients (range 23.5–26.3 h).
Isabella et al.	<i>N</i> = 42 (16UWS, 16MCS, 10 clinical control patients with severe tetraplegia)	Evaluate the distribution of sleep and wakefulness by means of polysomnography (EEG, EOG, EMG) and video recordings in patients.	All but one patient (UWS) showed behavioral and electrophysiological signs of sleep. 44% of UWS patients and 12% of MCS patients did not have any REM sleep, while all control patients (100%) showed signs of all sleep stages and sleep spindles.
Barbara et al.	<i>N</i> = 30 (hospitalized patients in the acute phase of moderate or severe TBI)	Consciousness level and cognitive functioning were assessed daily with the Rancho Los Amigos scale of cognitive functioning (RLA). Sleep and wake cycle characteristics were estimated with continuous wrist actigraphy. Mixed model analyses were performed on 233 days with the RLA (fixed effect) and sleep-wake variables (random effects).	Associations were found between scores on the consciousness/cognitive functioning scale and measures of sleep-wake cycle consolidation (<i>p</i> , 0.001), nighttime sleep duration (<i>p</i> = 0.018), and nighttime fragmentation index (<i>p</i> , 0.001). These associations showed strong linear relationships (<i>p</i> , 0.01 for all).
Gobert et al.	<i>N</i> = 16 (acute comatose)	Two biological urinary markers of CR were explored every 2 h during 24 h (6-sulfatoxymelatonin, free cortisol) with a dedicated methodology to extract the endogenous component of rhythmicity (environmental light recording, near-constant-routine protocol, control of beta-blockers).	They presented an initial absence of rhythmic secretions and a recovered CR 7–8 months later. This recovery was not associated with the restoration of behavioral wakefulness, but with an improvement of cognition and awareness (up to the minimally conscious state).

As part of a clinical examination, doctors judge a patient's level of consciousness by identifying how the eye reacts to stimuli and the pupil reacts light, as well as the direction of spontaneous eye movement (Ting et al., 2014).

Visual stimulation in scales

Over the years, through the efforts of researchers, multiple methods based on visual stimulation, like VP, VF, visual tracking, visual perception and other attributes, have been developed, with most studies indicating VP and VF to be the most effective and useful methods based on their unique advantages that include the ability to easily handle and observe them (Monti, 2012; Overbeek et al., 2018).

There is a large number of visual items in the Wessex Head Injury Matrix, which means that VP and VF are performed in different variations, depending on the exam paradigm. For example, different variations of each may require the participant to have their eyes opened but not focused on an object or a person, or perhaps the participant may be asked to look at a person attentively or watch a person moving for 3–5 s. These items range from low to high and are designed to reflect the progress of DOC patients using the Wessex Head Injury Matrix to assess the state of consciousness (Shiel et al., 2000). In comparison, in the Full Outline

of Unresponsiveness (FOUR) scale, the eye movement patterns are divided into four different states: eyelids open, tracking, or blinking when commanded; eyelids opened but not tracking; eyelids closed but opened upon hearing a loud voice; and eyelids closed but opened during sensory stimulation. The FOUR scale can be used to detect visual consciousness in the locked-in syndrome (Wijdicks, 2006). However, among the various assessment scales, the CRS-R is considered to be the “golden standard” (Seel et al., 2010). At present, the diagnosis of DOC patients are mainly based on behavioral assessments, and the CRS-R is the most widely used diagnostic tool for DOC assessment (Giacino et al., 2004). In the CRS-R, the visual function scale includes object recognition, object localization, visual pursuit, visual fixation and visual startle reflex. If the patient's eyes keep following a mirror with an angle of 45° in two of the four directions without looking away, then VP is present (Thonnard et al., 2014); while if patients manage to move their eyes from the initial fixation point to the target fixation point and hold a gaze at that point for more than 2 s in two of four trials, then VF exists (Ansell, 1995).

The application of VP and VF in the scale brings convenience to the diagnosis of DOC patients (Giacino et al., 2004); however, misdiagnosis still exists (Schnakers et al., 2009). For example Candelieri et al., 2011 (Candelieri et al., 2011) have found that of the patients diagnosed in a

vegetative state and MCS by the CRS-R, 63% of MCS patients had VP, only 33% of vegetative state patients had VP. Many other studies have indicated that it is not sufficient to diagnose DOC patients solely based on VP and VF, but the existence of VF can be seen as an indication of functional recovery (Stokes et al., 2018) and existence of VP indicates a better diagnostic effect in MCS than vegetative state patients (Schnakers et al., 2006).

Objective method applications

Besides behavioral tests, other methods with much more objectivity have been used to avoid misdiagnosis of DOC. Traditionally, visual assessments in DOC have been limited to simple eye responses assessments, which had many drawbacks, such as the results of tests depending largely on the experience of testers, which may have led to misdiagnoses. With the development of technology, we have access to more accurate methods of measuring eye movements than ever before, not just with the naked eye. Eye-tracking and recording technology, which appeared in the 1990s, requires sufficient time and spatial fidelity. Today, high-precision portable instruments have emerged, and eye movement monitoring has made great progress (De Santi et al., 2011; Trepagnier, 2002). Indeed, high throughput eye trackers have been used to evaluate eye movement in DOC patients. Trojano et al. (2012) conducted an experiment with nine vegetative state and MCS patients each and 11 healthy participants, using a new experimental device that combined stimulus detection with an eye movement recording device. Specifically, when the subject's eyes moved with the object, the device analyzed the coincidence degree of the stimulus's movement track and the subject's eye movement track and found that the on-target fixation proportion was different between MCS and UWS patients.

BCI is another ideal tool to assist consciousness assessment. Brain computer interface (BCI) was developed to assess the visual fixation in DOC patients because it directly detects the brain's response to external stimulus, independent of changes in behavioral indicators. EEG-based BCI can detect the brain's response to certain visual fixation. Therefore, the BCI may provide a promising method to assist behavior assessment. The proposed paradigm of the BCI system simulates the behavioral assessment of VF in the CRS-R, where the patient's eyes move from a starting point to a new target position and the patient is asked to hold the gaze at the final target position for more than 2 s. Each experiment begins with a 2-s period of cross-visual cues, with each patient's eyes guided by a brightly colored ball in the middle of a randomly selected target position from four directions; at the same time, the patient's EEG signals are collected. Results from 15 patients showed that one did not follow the ball in the CRS-R evaluation, but achieved significant online accuracy in the BCI evaluation. Therefore, a combination of the BCI and CRS-R can improve the accuracy of visual evaluation (Xiao et al., 2018).

Vestibulo-ocular response (VOR) is also widely used in the field of neuroimaging, and is based on the vestibulo-

ocular reflex. Traumatic brainstem injury often leads to alteration in brainstem functions, including the vestibulo-ocular reflex, so it is especially applicable to severe traumatic brain injury resulting in DOC (Schlosser et al., 2009). Normally, two types of stimulation can elicit a VOR: the traditional stimulation is to irrigate warm or cold water into the auditory canal unilaterally (Born et al., 1985; Jacob et al., 2010; Leigh et al., 1984; Levy & Plum, 1988; van den Berge et al., 1987; Weiss et al., 2012; Yagi & Baba, 1983), whereas the other nontraditional stimulation uses electrical stimulation, which is easier and safer to perform than the former (Schlosser et al., 2005). Weiss et al. have suggested that the presence of a fast component of nystagmus could predict accurately the emergence of patients' consciousness recovery. Another study using comatose state patients proposed that those with no responses to stimulation subsequently suffered brain death, whereas patients with a VOR later recovered (Schlosser et al., 2005).

The source of stimulus matters

During visual evaluations, the selected stimulus has a significant impact on the final diagnosis. Indeed, clinical scales often assess visual behavior using stimuli in response to a mirror (Ansell & Keenan, 1989; Estraneo et al., 2015), object, finger or person (Gill-Thwaites, 1997; Rappaport et al., 1992; Shiel et al., 2000). However, the mirror seems to be the most sensitive stimulus. Vanhaudenhuyse et al. have tested 38 MCS patients using the various methods just described and found 36 tracked moving mirrors, 25 who tracked moving people and 21 tracked moving objects, thus indicating that mirrors were tracked the most. The researchers believe that the difference between a person's VP of their face in a mirror and that of their face in a picture may have to do with the dynamic nature of the reflected image, which naturally causes smoother eye movements (Cruse et al., 2017; Vanhaudenhuyse et al., 2008).

In addition, some scholars suggested that images or objects that have to do with the patient can more significantly elicit their VPs. Wannez et al. (Wannez et al., 2017) have conducted a study in which 13 UWS, 13 MCS, and 13 healthy control participants used circles, pictures of parrots and pictures of their relatives as stimuli for VP and VF. The authors found that relatives' photographs attracted more attention than the other two stimuli in patients with an MCS, suggesting some image-related visual processing and emotional salience in MCS patients that was lacking in UWS patients (Trojano et al., 2012; Trojano et al., 2013).

Test challenges still exist

Visual assessments depend on the integrity of visual pathways, and many patients with impaired visual pathways are in the clinic. These patients may have potential brainstem damage that affects eye movement, which can limit their visual tracking and orientation (Naro et al., 2016). For example, although lack visual responses have been shown to be the most common symptom seen in MCS patients, a

deficiency in approximately 20% of MCS patients cannot be ignored (Estraneo et al., 2015). Therefore, for DOC patients with no visual responses, examination with techniques such as visual evoked potentials and imaging is suggested to check the integrity of the visual tract.

The use of visual assessments to accurately diagnose the level of consciousness is not easy, and the lack of internationally recognized assessments methods and standards lead to inconsistencies in assessment results. As a result, VP and VF do not yet constitute the gold standard in the visual evaluation of patients with consciousness disorders. In other words, the significance of VP and VF in relation to consciousness is controversial (Ting et al., 2014). However, many studies still consider them to be related to consciousness and regard them as the representation of MCS (Overbeek et al., 2018). At present, there is a lack of a standard for visual assessments of DOC patients and it is necessary to develop a recognized standard for such assessments.

Visual stimulation in treatment

CR as a target

CR was first discovered by Hall and colleagues, who the Nobel Prize in 2017 for their remarkable work on revealing the molecular mechanisms that control CR in organisms (Saper et al., 2005). CR is involved in a variety of basic function including photosynthesis, food intake, physiological process and learning and memory ability, all of which fluctuate with the day and night. Indeed, these alternating changes in human and other species follow 24-h cycle (Honma, 2018). Human physiological rhythms associated with CR can not only oscillate in the case of periodic changes in the environment, but also fluctuate in the absence of changes in the environment (Johnston et al., 2016). Over the past several decades, it has gradually been discovered that these changes in human body are controlled by specific brain circuits and neurotransmitters (Meijer et al., 2010). Specifically, light information is transmitted to the retina, after which non-imaging photoreceptors in the retina (intrinsic photosensitive retinal ganglion cells) project the information to the suprachiasmatic nucleus, which is known as the circadian pacemaker, as well as to other areas that regulate CR via the retinal hypothalamic tract to reset the pacemaker and affect the formation of individual rhythm (Schmidt et al., 2011). These events in turn change the time rhythm of behavior and physiological function such as the production of melatonin in the pineal gland, which directly affects the quality of sleep (Pfeffer et al., 2018; Rossi Sebastiano et al., 2015). Indeed, among the physiological processes affect by CR, sleeping pattern is the most observable and significant because normal sleep can be divided into two phases: non rapid eye movement sleep and rapid eye movement sleep (Fraize et al., 2016). The sleep-wake cycle of normal people is usually fixed and regular and is a necessary behavior to maintain survival, so as to ensure the normal high-level brain functions such as thinking, cognition and emotion (Li, 2014).

CR in DOC

The CR of normal people can be changed by external or internal factors, for example, the CR of night shift workers can be changed due to work scheduling (Drake et al., 2015), and Alzheimer's patients can also show different degrees of sleep cycle disorders (Grippe et al., 2015). These types of alterations are also found in DOC patients, but it is important to point out that disorder of CR in DOC patients is not the primary cause of the condition but recognized as a concomitant symptom (Arnaldi et al., 2016). According to the clinical DOC characteristics, most DOC patients often preserve arousal but lack the awareness of the outside world (Rossi Sebastiano et al., 2015; Seel et al., 2010). The movement of the patients' eyes is the most easily observed and recorded index to evaluate the sleep-wake cycle but not an accurate one, as the presence of an eye-opened/closed cycle may not indicate the existence of an electrophysiological sleep cycle (Cologan et al., 2013). For example, a study performed in 20 DOC patients indicated that while all patients showed a circadian, supracyclical or aperiodic sleep wake patterns, only a portion showed REMS (11/20, eight MCS and three UWS patients). Taken together, the results suggested that the general definition of wakefulness and sleep is not applicable to DOC patients (Cologan et al., 2013). Many studies are currently using polysomnography for circadian rhythm recording (Dominiak et al., 2021; Mertel et al., 2020; Rösler et al., 2023). Except for polysomnography, many studies also use wrist actigraphy as an indirect method that is highly correlated with polysomnographic estimates of sleep/wake cycles (Cruse et al., 2013; Mertel et al., 2020). Furthermore, various objective methods including body temperature (Blume et al., 2017) and melatonin concentrations in urine (Paparrigopoulos et al., 2006) have also been used to measure patients' CRs. In particular, melatonin concentrations in urine have consistently shown that a large majority of DOC patients do not have a typical sleep/wake cycle, especially UWS patients, who tend to have a significantly impaired sleep/wake cycle and who do not have a normal CR. Indeed it has been shown that UWS patients stay awake late at night but are drowsy during the day, or have short but frequent awake periods (Sinclair et al., 2014). The results indicate that DOC patients' CRs are severely altered and that UWS patients seem to have a more severely altered CR than MCS patients. Another study indicated that the recovery of consciousness was accompanied by a reorganization of the sleep/wake cycle, with improvements in both the cycle and sleep duration; furthermore, non-traumatic patients tended to have a more severely altered sleep/wake cycle than traumatic patients (Duclos et al., 2017).

Light therapy in DOC

The disruption of CRs can lead to a range of physiological and emotional disorders such as shortening the length of neuronal dendrites and decreasing the function of the pre-frontal cortex, which affect the brain's function of executing commands and controlling emotions, resulting in behavioral impulses and inability to concentrate (Lyll et al., 2018).

Night-shift workers face serious sleep problems because their long-term night work schedules, and application of melatonin or intermittent exposure to bright light and dark can help regulate and restore their CRs to regain a normal sleep pattern (Drake et al., 2015). As a reliable stimulus, visual stimulation is thought to be a promising intervention tool (Ansell, 1995; Candelieri et al., 2011; Cheng et al., 2018; Monti, 2012; Overbeek et al., 2018; Schnakers et al., 2006; Schnakers et al., 2009; Seel et al., 2010; Shiel et al., 2000; Thonnard et al., 2014; Wijdicks, 2006). However, the melatonin and intermittent light/dark exposure have only been recently introduced as treatments for DOC based on the advances in research on CRs (Yoo et al., 2014). Light therapy can effectively improve the CR of patients with non-conscious disorders, thus promoting the recovery of physical and mental functions. Interestingly, it has been shown that for DOC patients, a stable consciousness state is always accompanied a regular CR (Duclos et al., 2017; Sinclair et al., 2014); therefore, scientists suspect that as light therapy may help to restore normal CRs, it may also help to restore consciousness DOC patients in a noninvasive manner (Blume et al., 2017). Christine et al. have carried out a study involving 20 DOC patients to improve the patients' conscious states using strong light exposure at a certain time during the day. External skin sensors were used to record temperature data to calculate the circadian variations in body temperature and patients were divided into two groups with a protocol that covered two specific weeks. During week 1, the patients were exposed to habitual light conditions whereas during week 2, a subset of patients were then exposed to bright and blue light (≈ 2000 lux at eye level) three times a day (7 am, 1 pm, 7 pm) for 1 h. At the end of each week the CRS-R was performed and recorded by two trained experts. The results indicated that three of 20 patients showed enhanced behavioral modifications from an UWS to an MCS, and that the body temperature maximum of all three patients occurred closer to the times when it would be expected in healthy individuals (Blume et al., 2017), which occurs at about the same time as the circadian peak in cognition and arousal in healthy individuals (Sim et al., 2017). The study highlighted the potential role of light treatment in DOC patients, and also indicated a new study projecting that the time of assessment could be guided by the temperature rhythm of a specific patient to decrease the risk of misdiagnoses. However, the study had limitations including the limited sample size and causality between the recovery of CR and the conscious state could not be determined. Another recent study recorded the levels of urinary free cortisol and urinary 6-sulfatoxymelatonin to study altered CRs and found that recovery of CRs might be a prerequisite for recovery from a coma (Gobert et al., 2019). Further research is expected to be carried out with a larger sample size and assess patients with a more precise method such as fMRI. In addition, a direct link among neural connectivity, consciousness and CR is required to support the hypothesis.

Discussion

Visual stimulation has been used for diagnostic assistance in the field of DOC for several decades (Ting et al., 2014). Based on an in-depth understanding of visual physiology, visual stimulation plays a greater role in diagnosis. Initially, doctors assessed a patient's state of consciousness by observing the direction of spontaneous eye movements and the response to stimuli, among which, VP and VF were the most valuable and convenient to implement (Overbeek et al., 2018). VP and VF differ in the operation and diagnostic criteria of the various consciousness assessment scales. Since the CRS-R scale is the gold standard diagnostic tool for evaluating patients with DOC, VP and VF are often incorporated into the scale when assessing patients (Monti, 2012). Previous studies have found that lack of VP and VF can lead to the misdiagnosis of an MCS (Naro et al., 2016), which further illustrates the importance of visual stimulation. As technology evolves, researchers have begun to use eye movement monitors, brain-computer interfaces, vestibulo-ocular response and other tools to make more objective measurements and diagnoses. In the application of visual stimulation, the source of the stimulus needs to be paid attention to as the stimulus has a significant impact on the final diagnosis. As has been stated above, researchers believe that a mirror and/or object that a patient has personal attachment to significantly induces a visual response (Cruse et al., 2017; Vanhaudenhuyse et al., 2008).

Visual stimulation is not only used for diagnosis. In recent years, with the increasing attention paid to CR, visual stimulation has been applied in the form of light therapy to DOC patients with varying degrees of disturbance in the sleep/wake cycle. The vast majority of DOC patients have been shown to have significantly impaired sleep/wake cycles and that the restoration of consciousness is accompanied by improvements in sleep structure (Rossi Sebastiano et al., 2015); therefore, scientists suggest that a normal CR may help improve consciousness (Arnaldi et al., 2016). It has been shown that light therapy is effective at restoring normal circadian rhythms in night shift workers and Alzheimer's patients (Grippe et al., 2015). Light therapy is also often used in conjunction with polysomnography, wrist actigraphy, body temperature monitoring, eye movement tracking and urine melatonin content to estimate sleep/wake cycles and verify treatment effectiveness (Cruse et al., 2013; Paparrigopoulos et al., 2006). As far as experiments are concerned, light therapy can promote the conversion of UWS to MCS, with blue light having a better effect than other light wavelengths (Blume et al., 2017). Also of importance is the light intensity, light source distance and light duration. However, the light parameters selected in the experiments were all different, thus lacking a unified standard.

Although visual stimulation has been widely used in the study of in DOC, it is still controversial whether it can become an internationally recognized standard. VP and VF bring convenience to diagnosis and reduce the misdiagnosis rate, but due to the lack of unified operation methods and evaluation criteria, as well as the lack of objective evidence

to support the correlation between vision and consciousness, they are not enough to become the gold standard. We believe that the reason why VP and VF have not been standardized so far may be that the associated visual pathways and mechanisms have not been fully explored and understood, and studies on the correlation between vision and consciousness are lacking. The same problem exists in the development and application of light therapy, which has been shown to improve the disordered sleep/wake cycle in some DOC patients, but what constitutes "an appropriate improvement" still needs to be defined more clearly. In addition, experiments with small sample sizes have also reduced the persuasiveness of experimental results, which still need to be confirmed by a large number of clinical trials with larger samples. In the authors' opinion, light therapy is not yet available for clinical use for three reasons: (1) As an emerging potential treatment, light therapy does not have a long development period, and there are even fewer studies related to consciousness disorders. (2) The parameters of light treatment, such as light intensity and light duration, require long-term experiments with a large sample size. As far as we know, no such experiments have yet been completed. (3) Since the individual condition of each patient is unique, a unified experimental scheme may not work for each patient; researchers still need to set up specific programs for specific patients.

Based on the above discussion, we believe that there is a need to further improve the related visual pathways and mechanisms, and to explore the correlation between vision and consciousness. At the same time, the development and application of light therapy also need to be paid attention, but what is "appropriate improvement" still needs to be more clearly defined, and the number of samples should be increased to develop specific protocols for specific patients.

Conclusion

To the best of our knowledge, this is the first review to combine visual stimulation, CR and light therapy in DOC patients. Visual stimulation is widely used, especially in diagnosis and treatment. VP and VF have been broadly applied in various forms in different auxiliary diagnostic evaluation scales. However, whether VP and VF are related to consciousness remains controversial, and needs to be evaluated comprehensively with the help of objective evidence such as neuroimaging. The prevalence of CR disorders in DOC patients reduces the quality of life for patients and impedes their prognosis. Light therapy is a potential therapy developed in recent years. It has been applied in some other fields, but it is not mature in the field of DOC. At present, although visual stimulation and light therapy are frequently mentioned and applied, there is still no international unified standard. Therefore, we recommend international consensus regarding definitions, operational criteria and assessment procedures of visual stimulation and light therapy.

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