Steady-state visual evoked potentials as diagnostic tool for patients with severe disorders of consciousness - a proof of concept study

Martin J. Rosenfelder, L. Willacker, T. Olander, Andreas Bender, J. Dowsett

Angaben zur Veröffentlichung / Publication details:

Rosenfelder, Martin J., L. Willacker, T. Olander, Andreas Bender, and J. Dowsett. 2026. "Steady-state visual evoked potentials as diagnostic tool for patients with severe disorders of consciousness - a proof of concept study." *NeuroImage* 338: 122069. https://doi.org/10.1016/j.neuroimage.2026.122069.

NeuroImage 338 (2026) 122069

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Steady-state visual evoked potentials as diagnostic tool for patients with severe disorders of consciousness - A proof of concept study

M.J. Rosenfelder [a,b,c,d,*], L. Willacker [b], T. Olander [a], A. Bender [a,b,d,1], J. Dowsett [e,1]

[a] Therapiezentrum Burgau, Hospital for Neurological Rehabilitation, Burgau, Germany
[b] Department of Neurology, University Hospital of the Ludwig-Maximilians-Universität München, Marchioninistr. 15, Munich, Germany
[c] Clinical and Biological Psychology, Institute of Psychology and Education, Ulm University, Ulm, Germany
[d] Department Neurorehabilitation, Medical Faculty, University of Augsburg, Augsburg, Germany
[e] Division of Psychology, University of Stirling, Stirling, UK

ARTICLE INFO

Keywords:
Disorders of consciousness
Steady-state visual evoked potentials
Eeg oscillations
Visual flicker
Diagnosis

ABSTRACT

The diagnosis of disorders of consciousness (DoC) remains challenging with high rates of misdiagnoses, despite the development of new tools. We developed a new diagnostic paradigm using steady-state visual evoked potentials (SSVEPs) elicited by red-light visual flicker as a proxy for consciousness diagnosis. SSVEPs from 30 Hz and 40 Hz visual flicker stimulation, and the resulting effect on the dominant theta band electroencephalographic (EEG) frequency, were assessed in 13 DoC patients and 8 healthy participants. Analyses of the dominant EEG theta oscillation in 18 patients revealed a significant difference between coma/unresponsive wakefulness syndrome (UWS) and minimally conscious state (MCS) patients during 40 Hz visual flicker stimulation ($Z = -1.86$, $p = 0.031$, $d = -1.264$), but not during 30 Hz stimulation ($Z = 0.477$, $p = 0.317$, $d = 0.28$). Healthy awake participants showed larger SSVEPs at 40 Hz than 30 Hz, which is reversed in most DoC patients. The ratio of 30/40 Hz SSVEP amplitude was significantly different for healthy participants vs. coma/UWS patients ($Z = 2.674$, $p = 0.004$, $d = 2.669$) and MCS patients ($Z = 2.192$, $p = 0.014$, $d = 1.242$), respectively, but not for coma/UWS vs. MCS patients ($Z = 0.905$, $p = 0.183$, $d = 0.542$). Regarding level of significance, results were equal when using a single CRS-R assessment instead of the best out of five CRS-R assessments for diagnosis. We could show that 40 Hz visual flicker stimulation modulates the ongoing theta oscillations in DoC patients, and that the frequency specific properties of SSVEPs in DoC patients are significantly different from healthy participants, serving as a potential marker of consciousness.

1. Introduction

Disorders of consciousness (DoC) are states of altered consciousness caused by injury or malfunction of neural systems, which regulate arousal and awareness (Giacino et al., 2014; Posner and Rothbart, 2007). These range from coma (no eye-opening) and unresponsive wakefulness syndrome (UWS) where basic reflexes are preserved, (also known as vegetative state), to the minimally conscious state (MCS) with basic command following or signs of increased awareness (localization to pain, visual fixation or tracking, spontaneous verbalization) (Bruno et al., 2011; Giacino et al., 2002). Despite significant advances in medical technology, DoC patients can remain in UWS or MCS conditions, which may wax and wane (Giacino et al., 2002). Accurate diagnosis, prognosis, and consequent daily care represent a major challenge in clinical practice. It is estimated that up to 40% of DoC patients are misdiagnosed, especially where signs of consciousness are not recognized (Schnakers et al., 2009; van Erp et al., 2015). Dissociation between behaviour and brain function can drive to misdiagnosis, prognostic mistakes, ineffective rehabilitative approaches, and psychological stress in caregivers. In this regard, major efforts in the field have been focused on introducing functional neurodiagnostic tools to complement longitudinal behavioural assessment in order to improve diagnostic and prognostic accuracy (Kondziella et al., 2020; Willacker et al., 2022). Tools exploring the pathophysiological mechanisms of

* Corresponding author.
E-mail address: m.rosenfelder@therapiezentrum-burgau.de (M.J. Rosenfelder).
[1] These authors share senior authorship.

https://doi.org/10.1016/j.neuroimage.2026.122069
Received 30 June 2025; Received in revised form 3 June 2026; Accepted 19 June 2026
Available online 21 June 2026

DoC are e.g., based on neuroimaging, mainly functional magnetic resonance imaging (fMRI) and fluorodeoxyglucose-positron emission tomography - FDG-PET - (Owen et al., 2006), on electrophysiological grounded metrics (Comanducci et al., 2020; Engemann et al., 2018; Stefan et al., 2018), or biophysiological indices such as rate of spontaneous eye blinking (Magliacano et al., 2021) or nasal respiration (Arzi et al., 2020). For ethical, therapeutic, and economic reasons, it is crucial to determine consciousness diagnosis correctly and to predict outcome as early, reliably, and precisely as possible (Graf et al., 2008; Grill et al., 2013; Lopez-Rolon and Bender, 2015).

The recent guideline of the European Academy of Neurology on DoC considers multimodality of assessments an important element in DoC diagnostics (Kondziella et al., 2020). To further improve accuracy of diagnosis and prognosis it is thus important to investigate novel paradigms to reveal neuronal correlates of consciousness in DoC patients, which can add to the outcome of behavioural measures.

In particular, studies adopting EEG paradigms have made significant contributions in the field of DoC research. One of the key metrics of the EEG signal is its oscillatory activity, which represents the rhythmic activity of the brain at different frequencies. These different rhythms can be linked to specific brain states and cognitive processes and have been reported to be altered in DoC patients. EEG studies typically investigate either the endogenous neural oscillations across various frequency bands spontaneously produced by the brain (Bai et al., 2017; Duszyk-Bogorodzka et al., 2022), or the evoked activity produced by a specific stimulus - e.g. evoked-related potentials, ERPs - (Kotchoubey, 2017). A specific type of evoked analysis, which can be used to investigate the frequency specific neural response is the so-called Steady State Visually Evoked Potential (SSVEP), which is the neural response to a flickering light source at a specific frequency (Norcia et al., 2015). It has been shown that the visual cortex can respond to visual flicker at frequencies from 1–100 Hz, showing particular resonance at neurologically relevant frequencies of 10, 20 and 40 Hz (Herrmann, 2001). The evoked response created by averaging many segments of data time-locked to the visual flicker can result in exceptionally high signal to noise ratio, as any sources of noise not time locked to the flicker (e.g. muscle artifacts, eye movements) will eventually be reduced to zero in the process of averaging if data is recorded for sufficient length of time (e.g. 3.5 min) (Dowsett et al., 2020).

Resonance in the cortex resulting from 40 Hz visual stimulation is of particular interest as links between gamma band activity (30 - 80 Hz) and consciousness have been reported; for example animal research has shown that during ketamine anesthesia high frequency oscillations in the gamma range are altered (Garwood et al., 2021; Mainali et al., 2022). In humans, decreased gamma oscillations have been associated with cognitive decline in a range of neurological and neuropsychiatric disorders, such as Alzheimer's disease (He et al., 2021; Sahu and Tseng, 2023; Strüber and Herrmann, 2020). Accordingly, the therapeutic effects of gamma entrainment on cognitive functioning through non-invasive brain stimulation are being increasingly investigated (Strüber and Herrmann, 2020). Sensory entrainment stimulation, which presents flickering light or sounds at gamma frequencies, can induce gamma oscillations in the auditory (Pantev et al., 1991; Pastor et al., 2002) and visual cortices (Herrmann, 2001) of healthy brains (Strüber and Herrmann, 2020). Moreover, such 40 Hz stimulation has been found to attenuate amyloid pathology and improve cognitive capacities in both AD patients and mouse models (Adaikkan et al., 2019; He et al., 2021; Iaccarino et al., 2016; Martorell et al., 2019; Sahu and Tseng, 2023; Singer et al., 2018) while being safe and tolerable, even when presented for prolonged periods of one hour daily for 4–8 weeks (He et al., 2021).

In this study we tested if SSVEPs in the gamma band at 30 Hz and 40 Hz could provoke a brain response that was (1) different between healthy controls and DoC patients, and more importantly (2) different between patients with UWS and MCS, thus qualifying as a biomarker of consciousness in the severely injured brain. As 40 Hz stimulation is particularly linked to consciousness - as shown above - we hypothesized that the difference in SSVEPs resulting from 40 Hz and 30 Hz visual flicker stimulation would be more dissociable in MCS patients than the UWS patients, accounting for their reduced state of consciousness compared to MCS patients.

We looked at the ratio of the amplitude at 30 Hz and 40 Hz, as we hypothesized that the higher amplitude at 40 Hz (relative to 30 Hz) typically seen in healthy participants might be an index of consciousness. The ratio of 40 Hz to 30 Hz might be a particularly useful measure as SSVEP amplitude can vary significantly across participants, and across experimental setups (different amplifiers and electrode types etc.). The comparison of SSVEPs at two different frequencies gives a baseline response which can correct for variability across participants and different setups.

Our main hypothesis was that there would be a significant difference in the amplitude of the 40 Hz SSVEP relative to the 30 Hz SSVEP, as resonance at 40 Hz is associated with conscious perception. In addition to our primary hypothesis we performed an exploratory analysis on various aspects of the 30 and 40 Hz SSVEPs to identify optimal markers of consciousness.

We chose to compare 30 and 40 Hz as these two frequencies produce a fairly similar perceptual response, but often result in distinct differences in the SSVEP in healthy participants; with the resonance at 40 Hz being of particular interest as this may be related to the activity of neural circuits associated with consciousness (Başar-Eroglu et al., 1996; Llinás & Ribary, 1992; Tassi & Muzet, 2001).

As well as the evoked SSVEP response, we also investigated the effect of the visual flicker stimulation on the endogenous dominant oscillations commonly observed in DoC patients. The endogeneous oscillations in DoC patients are characterized by predominant delta oscillations in most UWS patients, and a higher theta band power in DoC (UWS and MCS) patients compared to healthy controls (Bai et al., 2021). Theta power is also strongly correlated with clinical behavior (Bareham et al., 2020). Endogeneous dominant oscillations are patient-specific, but can be expected to be either delta or theta frequencies. We hypothesized that 40 Hz stimulation might have a distinct effect on the ongoing oscillatory activity, which could potentially provide an additional diagnostic measure.

2. Materials and methods

2.1. Participants

20 DoC patients (15 male, 5 female) and 8 healthy control subjects (6 male, 2 female) have been recruited for this study at a neurorehabilitation hospital in the south of Germany (Therapiezentrum Burgau, Bavaria, Germany). DoC patients in coma, UWS, MCS and eMCS were included. Patients were not included if they showed signs of epilepsy (epileptic discharges in the EEG) or if they had ongoing seizures that were not medically treated. There was no patient that had to be excluded due to epilepsy. Demographic and anamnestic data of patients and healthy controls groups can be found in Table 1. Details of individual subjects are shown in Table 1 of the supplementary material. Healthy participants provided informed consent to participation. For DoC patients, informed consent was obtained by the respective legal guardian. The ethics committee of the medical faculty at Munich university approved this study (No. 20–635), which was conducted as later amended part of an EU-funded clinical trial (EraPerMed), that is registered at ClinicalTrials.gov (NCT04798456).

2.2. Clinical evaluation of doc patients

The clinical evaluation of the state of consciousness was evaluated at the beginning of the session for each DoC patient, using the Coma Recovery Scale-revised (Giacino et al., 2004) by an experienced rater. The Coma Recovery Scale Revised (CRS-R) is a standardised and

Table 1
Demographic and anamnestic data of patients and healthy control subjects.

	Coma (n = 1) and UWS (n = 8)	MCS (n = 10) and eMCS (n = 1)	Healthy controls	p-value
Gender - male: female	7:2	8:3	6:2	1
Age - M(SD)	50.9(17.4)	51.8(15.5)	33(8.3)	.024
Time post injury (days) - M (SD)	517.7(1219.5)	261.1(437.8)	-	.676
TBI:non-TBI	3/6	3/8	-	1
CRS-R total scores M(SD)	6.3(1.7)	12.7(3.0)	-	< 0.001

Note. UWS = unresponsive wakefulness syndrome, MCS = minimally conscious state, eMCS = emergence from minimally conscious state. TBI = traumatic brain injury, M = mean, SD = standard deviation. The diagnosis (Coma, UWS, MCS) reflects the best diagnosis within two weeks according to five assessments with the Coma Recovery Scale - Revised.

multidimensional behavioral scale that is used most in diagnostics of DoC patients (Schnakers et al., 2009). It consists of 23 items arranged hierarchically and divided into six subscales (auditory, visual, motor, oromotor / verbal, communication and arousal). The score on each subscale is based on the presence or absence of behavior in response to sensory stimulation. The diagnosis is based on the nature of the best responses observed in each subscale. In several international validation studies, the CRS-R demonstrated good to excellent diagnostic sensitivity, internal consistency and criterion validity as well as intra- and interrater reliability (Giacino et al., 2004; Maurer-Karattup et al., 2010).

2.3. Visual flicker stimulation

To deliver visual flicker stimulation, an evoked potential system (Neuropack M1) from Nihon Kohden (Nihon Kohden Europe GmbH, Rosbach, Germany) was used. The system generated a sequence of red flashing LED light that was delivered to the eyes through a pair of goggles (Fig. 1). SSVEPs at 40 Hz have been previously recorded during sleep with red light flicker built into a sleep mask (Hainke et al., 2025). This makes them optimal for stimulation in DoC patients, who are characterized by fluctuating arousal (Wislowska et al., 2017). Red light has been reported to be optimal regarding perceived brightness with closed eyes (Bierman et al., 2011; Sakai, 2023). This visual flicker was presented to the left and right eye simultaneously through 10 red LEDs per eye. The goggles were placed over the eyes and fixed with a rubber band behind the head to ensure that the goggles were firmly placed on the eyes and surrounding light was blocked from entering the setup. Patients were tested lying in the bed on their back, healthy participants were seated in a chair in a comfortable position, slightly leaned backwards.

2.4. Creating SSVEPs

Creating SSVEPs with a high signal-to-noise ratio requires triggers in the EEG recording that are exactly time locked to the visual flicker. As the visual stimulation device used in this study did not have a trigger function, we built a custom circuit to generate triggers. This consisted of a photodiode placed inside the eye mask which recorded the change in luminance and generated a trigger in the EEG recording exactly time locked to the flicker. This allowed us to average thousands of segments of data (e.g. 40 Hz * 600 s = 24,000 segments in 10 min) to create an evoked response with a very high signal to noise ratio. This has the advantage of giving a very clean signal, but has the disadvantage of also being very sensitive to technical artifacts. As the flicker device is fitted over the eyes it is very close to the sensitive EEG electrodes and causes an electrical artifact in the signal, which can be mistaken for neural activity. To control for this, we carried out the experiment on several healthy participants with the addition of a "blackout" condition where the participant was wearing a blindfold between eyes and goggles such that no light could reach the eye, but otherwise the setup was identical. This allows us to quantify and remove any technical artifacts. In this setup, and in most other similar setups, we see a spike in the data at the point where the light switches on, and a spike in the opposite direction when the light switches off. This is an induced electromagnetic signal caused by the change in current. Although this artefact can be quite large, it is brief; typically, a few milliseconds. In cases such as this we can remove the artifact with linear interpolation of the signal over this brief time period. This is commonly used for transcranial magnetic stimulation artifact removal. Fig. 2 shows SSVEPs from a healthy participant at 30 and 40 Hz, with and without a blindfold. One can clearly see the "spikes" in the data when the light switches on and off in both conditions. The (approximately) sinusoidal SSVEP can be seen without the blindfold, with the electrical artifact superimposed on the neural response. Below is the same data after the artifact removal. The linear interpolation replaces the segment of data during the "spike" with a straight line fitted to the data immediately before and after the artifact. We can see in the blackout data after artifact removal a near flat line, which is what we would expect to see if there were no electrical artifacts (because there is no neural activity time locked to the visual flicker). As we are creating SSVEPs by averaging segments of data time locked to the visual flicker, we know that these artifacts will be in exactly the same point relative to the trigger, and can apply the same removal procedure to all data. Visual inspection confirmed that no residual artifacts were remaining in the data across all DoC patients and healthy controls.

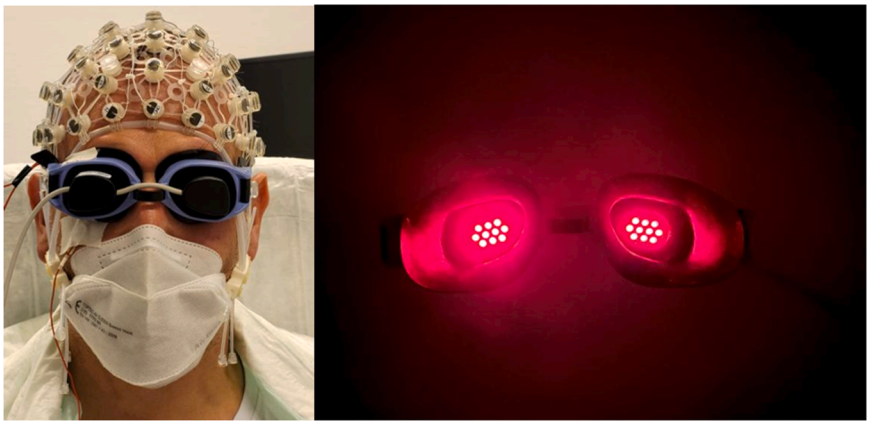

Fig. 1. Healthy participant with goggles delivering visual flicker, photodiode and 64-channel electroencephalography (EEG) system (left). Inside of the goggles with 10 red LEDs per eye (right).

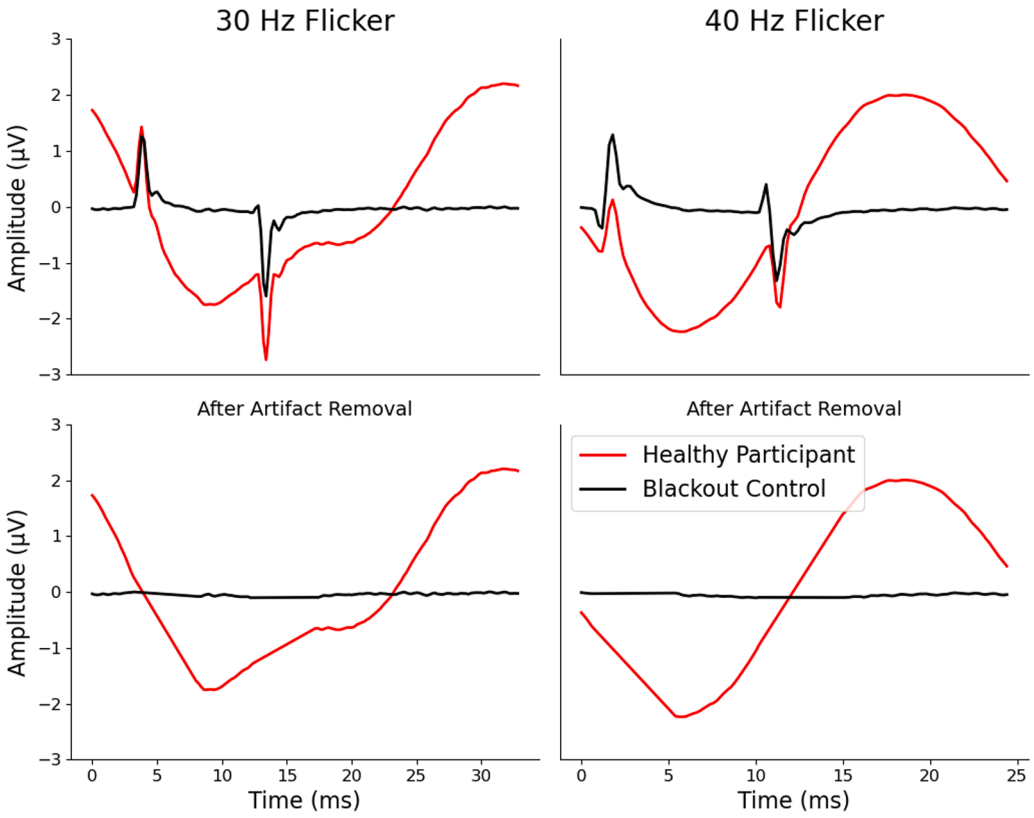

Fig. 2. SSVEPs in a healthy participant at 30 Hz and 40 Hz visual flicker frequency before (upper row) and after (lower row) artifact removal. Red lines display the evoked potential during stimulation when the visual flicker can enter the eye (typical setup also used in DoC patients). Black lines show the evoked potential during stimulation when the visual flicker is blocked from entering the eye by shielding with black cardboard that has been placed between the red LEDs and the participant's eyes.

2.5. EEG recording

EEG recording was done in all subjects (patients and healthy participants) with a 64-channel EEG system (BrainAmp DC, BrainProducts, Gilching, Germany) and an electrode cap with saline-soaked sponges (R-Net, EasyCap, Wörthsee, Germany). The BrainAmp DC applies a 0.1 Hz low cut-off and a 1000 Hz high cut-off hardware filter to the recorded EEG signal. There was no notch recording filter. EEG data were recorded at rest for five minutes prior to the visual flicker stimulation, and for ten minutes at 30 Hz and another ten minutes at 40 Hz during visual flicker stimulation. Patients and healthy participants were instructed to remain still, but not to fall asleep during the procedure. An advantage of using red light LED goggles for visual flicker presentation is that stimulation functions regardless of whether the eyes are open or closed. Thus, DoC patients did not need to be specifically instructed to keep their eyes open or closed. Patients were monitored during the recording procedure by a researcher and a study nurse regarding any abnormal EEG activity - including ictal activity. EEG data was sampled at 5000 Hz, without additional recording filters.

2.6. EEG preprocessing

All EEG analyses were done in python using a combination of MNE (Gramfort et al., 2013) and custom written scripts.

We successfully recorded SSVEPs with time locked triggers (using the photodiode method described above) from all DoC patients at 30 Hz and 40 Hz, for 10 min each. The order was kept the same because our primary output measure was the online effect of flicker stimulation. Keeping the stimulation procedure constant allowed for a direct comparison between patient groups. We also repeated the same experiment in 8 healthy control subjects. We used electrode POz for SSVEP and EEG dominant frequency analyses, as this typically shows a high response to visual flicker (Dowsett et al., 2020). Data was cleaned using the linear interpolation method described above. No other filters were applied (e.g. high-pass filter), as there was no drift in the EEG signal. Data was segmented into 500 ms segments time locked to the trigger corresponding to the onset on the light. Segments were non-overlapping, with each subsequent segment being time locked to the next trigger not included in the 500 ms segment of data (Herrmann, 2001). This resulted in approximately 1200 segments of data for each 10 min trial. Segments were then averaged, baseline corrected and multiplied by a hanning window; finally, a fast fourier transformation (FFT) was applied to the averaged signal to give the final SSVEP in the frequency domain.

2.7. SSVEP extraction

Due to technical failure of the photodoide, SSVEPs could only be extracted from n = 13 DoC patients (see Table 2 in the supplementary material for the excluded patients P1, P4, P6, P7, P10, P12, P13), with n = 9 MCS/eMCS and n = 4 coma/UWS patients for the best CRS-R score analysis and n = 6 MCS/eMCS and n = 7 coma/UWS patients for the single CRS-R score analysis. We looked at the peak amplitude of the SSVEPs at 30 and 40 Hz. SSVEPs are often non-sinusoidal and typically show peaks in the frequency spectrum at harmonics, e.g. at 40 Hz we see peaks at 40, 80, 120, 160 Hz etc. These peaks can be either the result of higher frequencies being evoked by the flicker, or by the SSVEP being non-sinusoidal in shape with steep rise/fall of the signal resulting in higher harmonics. We also looked at the ratio of the fundamental frequency to the first harmonic (e.g. the amplitude of the peak at 40 Hz divided by the amplitude of the peak at 80 Hz), as an index of waveform shape which might be correlated with consciousness. We often see in healthy participants more complex waveform shapes from lower

Table 2
Exploratory tests on the effect of 30 Hz and 40 Hz visual flicker on various outcome measures (peak at visual flicker frequency, ratio of fundamental to 2nd harmonic, ratio of 30/40 Hz peak) with diagnosis taken from the best CRS-R assessment within two weeks.

Flicker frequency	Measure	Comparison	Z score	p-value	Effect-size
30 Hz	Peak at flicker frequency	HC vs. coma/UWS	1.791	0.037*	1.241
30 Hz	Peak at flicker frequency	HC vs. MCS/eMCS	1.465	0.071	0.729
30 Hz	Peak at flicker frequency	coma/UWS vs. MCS/eMCS	1.334	0.091	0.84
40 Hz	Peak at flicker frequency	HC vs. coma/UWS	2.652	0.004**	2.535
40 Hz	Peak at flicker frequency	HC vs. MCS/eMCS	2.547	0.005**	1.547
40 Hz	Peak at flicker frequency	coma/UWS vs. MCS/eMCS	1.204	0.114	0.734
30 Hz	Ratio of fundamental to 2nd harmonic	HC vs. coma/UWS	1.57	0.058	1.036
30 Hz	Ratio of fundamental to 2nd harmonic	HC vs. MCS/eMCS	2.134	0.016*	1.18
30 Hz	Ratio of fundamental to 2nd harmonic	coma/UWS vs. MCS/eMCS	0.994	0.16	0.596
40 Hz	Ratio of fundamental to 2nd harmonic	HC vs. coma/UWS	1.489	0.068	0.975
40 Hz	Ratio of fundamental to 2nd harmonic	HC vs. MCS/eMCS	1.734	0.041*	0.895
40 Hz	Ratio of fundamental to 2nd harmonic	coma/UWS vs. MCS/eMCS	0.322	0.374	0.198
30+40 Hz	Ratio of 30/40 Hz peak	HC vs. coma/UWS	2.688	0.004**	2.669
30+40 Hz	Ratio of 30/40 Hz peak	HC vs. MCS/eMCS	2.202	0.014*	1.242
30+40 Hz	Ratio of 30/40 Hz peak	coma/UWS vs. MCS/eMCS	0.898	0.185	0.542

Note. Test results are shown for three subgroup comparisons: healthy participants vs. coma/unresponsive wakefulness patients (denoted as UWS), healthy participants vs. minimally conscious state/emergence from minimally conscious state patients (denoted as MCS), and coma/UWS vs. MCS/eMCS patients. All p-values are uncorrected due to the exploratory nature of the statistical tests.
* p-values < 0.05.
** p-values < 0.01.

frequencies of visual flicker resulting in larger harmonics; for example a higher second harmonic from 30 Hz flicker (60 Hz) than from 40 Hz flicker (80 Hz).

2.8. Calculating frequency and power of the dominant oscillation

For the analysis of the effect of visual flicker on the dominant theta oscillations, the data from electrode POz was selected and epoched into 5 s, non-overlapping segments (approximately 120 segments from each 10-minute recording). Each segment was baseline corrected, multiplied by a hanning window and an FFT was performed on each. The resulting spectra were then averaged to create one spectrum for each condition (30 Hz flicker, 40 Hz flicker and baseline) for each patient with a frequency resolution of 0.2 Hz. Induced frequency spectra of neural activity typically contain an aperiodic component (often called the 1/f noise) which is superimposed over any periodic components (i.e. the oscillations) and can distort the amplitude of these oscillations (Donoghue et al., 2020). We used the FOOOF (fitting oscillations & one over f) toolbox to remove the aperiodic component, as this can vary between participants due to noise, and recover the amplitude of the dominant oscillation. Patients who did not show any clear oscillatory activity above the 1/f aperiodic noise were excluded from this analysis (n = 2, P2, P14, see Table 2 in the Supplementary Material). All other patients (n = 18) exhibited a clear dominant oscillation in the theta range (mean frequency: 5.8 Hz, standard deviation: 2.15 Hz). The FOOOF algorithm was set to identify peaks in the data between 0 and 20 Hz; the dominant oscillation was identified by eye and the corresponding corrected power from the FOOOF algorithm was extracted for each condition. To normalize for each patient, the power of the dominant oscillations in the baseline condition was subtracted from the power of the dominant oscillation during both the 30 Hz and 40 Hz flicker. DoC patients were separated into two groups: coma/UWS (n = 10) and MCS (n = 8) for single CRS-R diagnosis and n = 11 and n = 7 for the best CRS-R diagnosis, respectively. Details on frequency and power of the dominant oscillation can be found in Table 2 of the supplementary material. A permutation test was performed for both the 30 Hz and 40 Hz conditions comparing the effect of the visual stimulation on the power of the dominant theta oscillation between coma/UWS and MCS groups, and effect size was reported as Cohen's d.

As expected, healthy participants did not show any dominant oscillation in the theta range, only the typical alpha oscillation (8–14 Hz). As the healthy alpha rhythm behaves very differently to the pathological theta rhythm (especially as a result of visual stimulation), and likely has distinct physiological origins, it is not comparable to pathological theta waves and no comparisons were made.

2.9. Statistical analyses

As numbers in the DoC groups (coma, UWS, MCS) were small, two groups of patients were created for statistical analyses: coma and UWS patients were compared against MCS and eMCS patients. This allowed for statistical testing with higher power, using nonparametric permutation tests (Cohen, 2017) implemented in custom Python code.

3. Results

3.1. Effect of visual flicker frequency on SSVEPs

3.1.1. Analyses with the best clinical diagnosis within two weeks

Our primary hypothesis that the ratio of the amplitude of the 30/40 Hz SSVEP peaks would be significantly different for conscious healthy controls and DoC patients was confirmed with both coma/UWS and MCS/eMCS groups showing a significant difference to healthy controls. On average the healthy controls showed a higher peak at 40 Hz than 30 Hz, whereas on average the DoC patients showed the opposite effect with a higher peak at 30 Hz (see Figs. 3 and 4). Specifically, the ratio of 30/40 Hz SSVEP amplitude was significantly different for healthy controls vs. coma/UWS patients ($Z = 2.674$, $p = 0.004$, $d = 2.669$) and for healthy controls vs. MCS/eMCS patients ($Z = 2.192$, $p = 0.014$, $d = 1.242$). The effect size was large in both cases, but noticeably larger for healthy controls vs. coma/UWS patients. The comparison between coma/UWS and MCS/eMCS groups did not reach significance ($Z = 0.905$, $p = 0.183$, $d = 0.542$).

3.1.2. Analyses with clinical diagnosis at the day of visual flicker stimulation

The results of the effect of the visual flicker frequency on the SSVEPs with clinical diagnosis on the day were identical to the results using the best clinical diagnosis within two weeks. For further reference regarding the results on the day, see Supplementary Material 1.

3.2. Effect of visual flicker stimulation on EEG dominant frequency

3.2.1. Analyses with the best clinical diagnosis within two weeks

The mean difference in power was negative during 30 Hz flicker for both coma/UWS ($-0.001\ \mu V^2$) and MCS/eMCS ($-0.022\ \mu V^2$) groups, i.e. the visual stimulation resulted in a reduction in power of the dominant

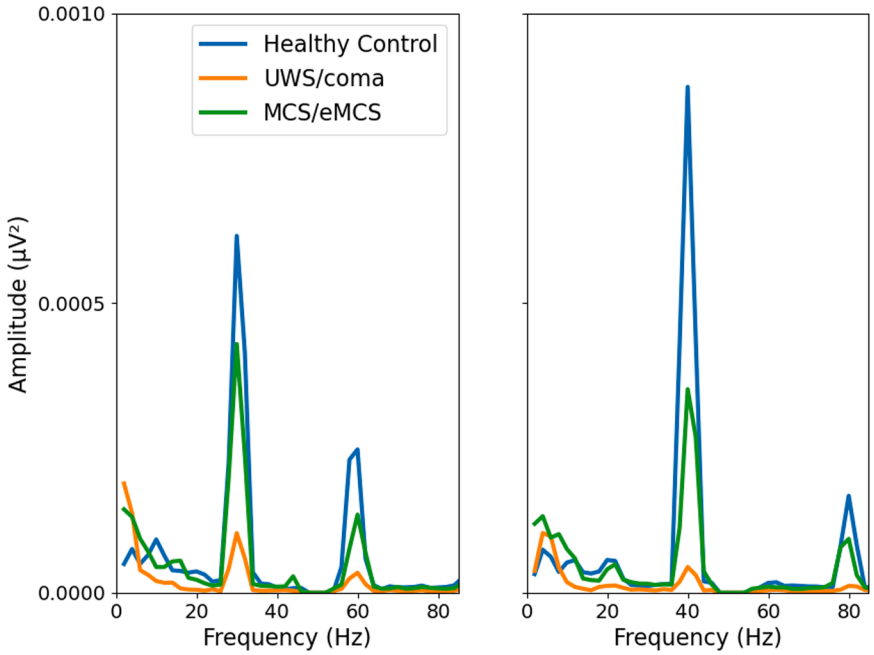

Fig. 3. Evoked FFT showing SSVEPs, averaged across all participants/patients, for 30 Hz (left) and 40 Hz (right) flicker. A clear peak at the flicker frequency and the 2nd harmonic can be seen in all cases. For the healthy controls the 40 Hz flicker evokes a larger response, and the 30 Hz flicker evokes a larger 2nd harmonic relative to the peak at the fundamental. Both DoC groups show weaker SSVEP amplitudes than healthy controls generally, with 40 Hz being smaller on average than 30 Hz. The scaling of the y axis is of the same amplitude in both plots. UWS = unresponsive wakefulness syndrome. MCS = minimally conscious state. eMCS = emergence from minimally conscious state.

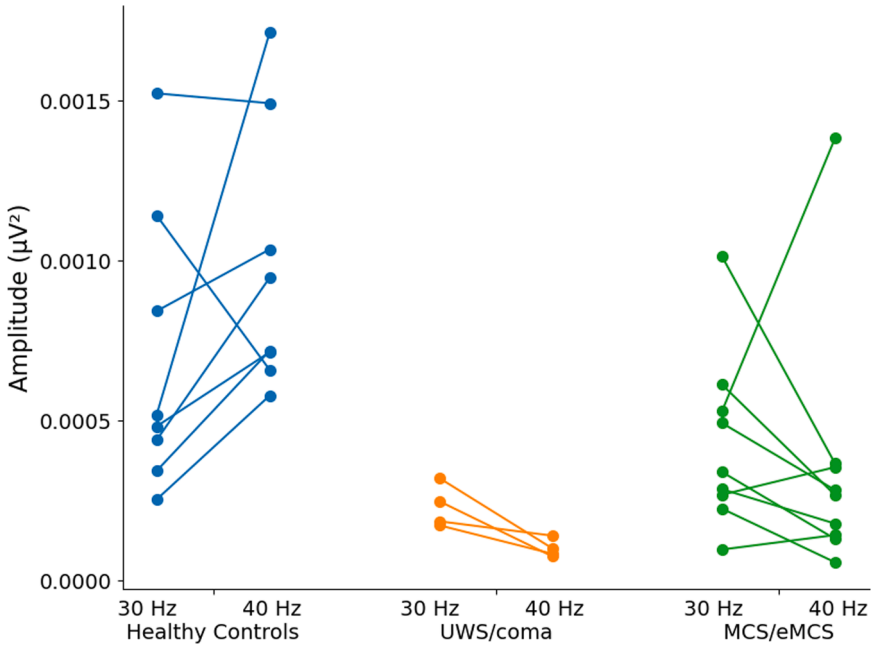

Fig. 4. Peak amplitude of SSVEPs for each participant/patient for 30 Hz and 40 Hz flicker. For most (but not all) healthy participants the 40 Hz peak was larger than the 30 Hz, whereas the opposite is true for most (but not all) DoC patients. UWS = unresponsive wakefulness syndrome. MCS = minimally conscious state. eMCS = emergence from minimally conscious state.

theta oscillation relative to baseline on average. All coma/UWS patients showed a decrease in the change of dominant frequency power (visual flicker - baseline) from 30 Hz to 40 Hz visual flicker. MCS/eMCS patients present a mixture of decrease and increase in the change of dominant frequency power (visual flicker - baseline) from 30 Hz to 40 Hz stimulation (Fig. 5).

Likewise, the mean difference in power during 40 Hz flicker was negative for both the coma/UWS group ($-0.074\ \mu V^2$) and the MCS/eMCS group ($-0.006\ \mu V^2$).

The permutation tests revealed no significant difference between coma/UWS and MCS/eMCS patients for 30 Hz visual stimulation ($Z = 0.477$, $p = 0.317$, $d = 0.28$). However, we did observe a significant difference between MCS/eMCS and coma/UWS groups during 40 Hz visual stimulation ($Z = -1.86$, $p = 0.031$, $d = -1.264$), see Fig. 5.

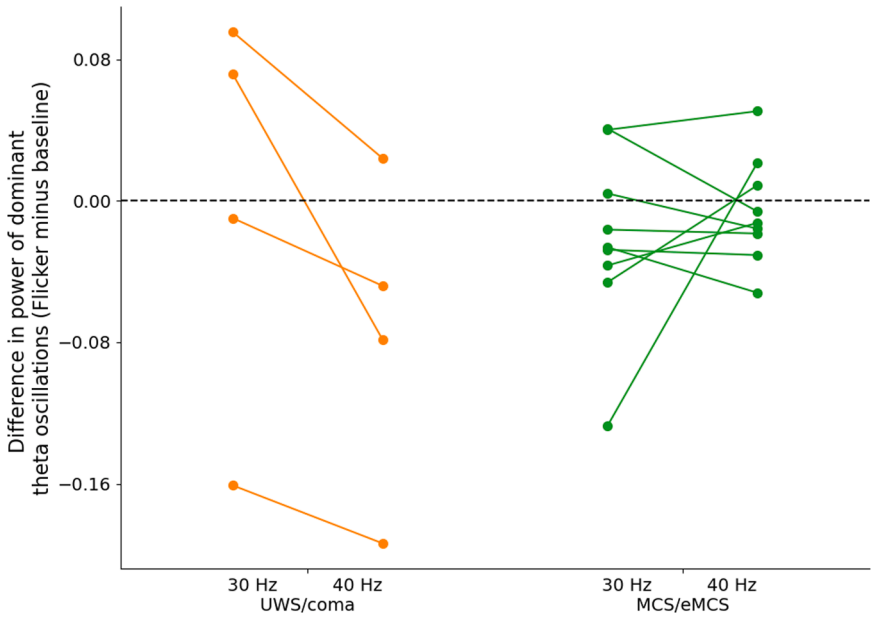

Fig. 5. Difference in absolute EEG signal power of the dominant theta frequency between baseline and visual flicker stimulation in coma/unresponsive wakefulness (UWS) patients and minimally conscious state (MCS) / emergence from minimally conscious state (eMCS) patients.

We did an exploratory analysis without the two patients in coma and eMCS to see if effects still hold if only UWS and MCS patients remain in the sample. For the remaining 16 subjects the mean difference in power (visual flicker - baseline) remained negative for 30 Hz (UWS: −0.011; MCS: −0.022) and 40 Hz stimulation (UWS: −0.054; MCS: −0.005). There was no significant difference between UWS and MCS patients for 30 Hz stimulation ($Z = 0.288$, $p = 0.387$, $d = 0.152$) and 40 Hz stimulation ($Z = -1.325$, $p = 0.093$, $d = -0.794$).

3.2.2. Analyses with clinical diagnosis at the day of visual flicker stimulation

When classifying DoC patients using the best clinical diagnosis within two weeks, we observed similar results from the effect of the stimulation on the endogenous frequency. Details can be found in the Supplementary Material 2.

3.3. Exploratory analyses

3.3.1. Analyses with the best clinical diagnosis within two weeks

Table 2 shows the results of all exploratory tests (uncorrected p-values are shown for reference only). The amplitude of the peak at flicker frequency was higher in healthy participants compared to both groups of DoC patients for both 30 and 40 Hz flicker, although 40 Hz had the largest effect size ($d = 2.535$ for UWS/coma, $d = 1.547$ for MCS/eMCS). The ratio of the fundamental to the 2nd harmonic (i.e. the non-sinusoidal characteristics of the waveform shape) resulted in large effects sizes (>1) with 30 Hz flicker when comparing healthy participants to both coma/UWS patients, and MCS/eMCS patients.

3.3.2. Analyses with clinical diagnosis at the day of visual flicker stimulation

Table 3 in the Supplementary Material shows the results of all exploratory tests (uncorrected p values are shown for reference only). The amplitude of the peak at flicker frequency was higher in healthy participants compared to both groups of DoC patients for both 30 and 40 Hz flicker, although 40 Hz had the largest effect size ($d = 2.634$). All effect sizes were comparable to those from the analyses using the best clinical diagnosis within two weeks.

4. Discussion

In this study we sought to investigate the effect of visual flicker stimulation on SSVEPs and the dominant EEG oscillationsin DoC patients. Studying these effects in 13, respectively 18 DoC patients and 8 healthy participants, we were able to confirm our primary hypothesis; namely that the amplitude ratio between the 30 Hz and 40 Hz SSVEPs was significantly different between healthy awake participants and DoC patients. As far as we are aware, we are the first to record gamma band SSVEPs in DoC patients and an exploratory analysis was justified to seek out potential markers which might be able to distinguish states of consciousness, and in particular to separate cases of coma/UWS and MCS/eMCS. Although no SSVEP measure reached statistical significance when directly comparing coma/UWS and MCS/eMCS patients, and this was a relatively small sample size, some effects (e.g. ratio of 30 to 40 Hs peak) gave effect sizes of greater than 0.7. The limited sample size might be the primary reason for the effect in the 30/40 Hz peak ratio between UWS and MCS patients not reaching statistical significance. Further studies with a larger sample size are justified, as well as further exploration of the optimal stimulation parameters to distinguish different states of consciousness.

We were able to observe a difference between coma/UWS and MCS/eMCS patients in the effect of 40 Hz visual flicker on the amplitude of the endogenous theta oscillations. As this was a small sample size, and the effect was subtle, this result should be interpreted with caution, but further investigation is justified. It has to be noted that when coma and eMCS patients are removed from the sample, the effect of the visual flicker stimulation on the theta oscillations is no longer significant (but does trend towards significance). Interestingly, coma and eMCS patients tended to drive the effect. Further studies with a greater number of patients in the various subgroups are warranted to investigate this finding in more depth. We do not have a clear hypothesis as to why the amplitude of the endogenous theta oscillations would be affected by gamma band visual flicker, but as 40 Hz stimulation has been reported to have a wide range of neural effects in both humans and mice, e.g. strengthening of neuronal connectivity and synaptic plasticity (You et al., 2020; Zheng et al., 2020), as well as glymphatic, neuroimmune and vascular effects (Blanco-Duque et al., 2024; Murdock et al., 2024), it is reasonable to assume a change in global brain state can result from such frequency specific stimulation that might affect the pathological

theta oscillation.

There was one UWS patient (P4) who showed an increase in power in the dominant (theta) oscillation from 30 Hz to 40 Hz visual flicker stimulation, contrary to all other patients in that group (see Fig. 3 in the Supplementary Material). Approximately one week prior to the visual flicker stimulation, this patient was diagnosed with MCS, due to command-following behavior (opening and closing the eyes and squeezing the investigator's hand on command). Thus, despite being clinically unresponsive on the day of investigation, the pattern of an increase in dominant frequency power from 30 Hz to 40 Hz resembled an MCS patient, which was the 'true' state of consciousness of this patient when assessed with the best CRS-R out of multiple assessments. For another UWS patient (P15), the 40 Hz SSVEP amplitude was larger than the 30 Hz peak amplitude, which was reversed in all other coma/UWS patients. Thus, the SSVEP pattern of this one UWS patient mimics the pattern of most MCS patients and healthy control participants (see Fig. 2 in the Supplementary Materials). Indeed, only one week after the assessment of SSVEPs, this patient was clinically diagnosed with MCS due to visual pursuit behavior, and fitted the pattern of other MCS patients in the analysis with the best CRS-R score (Fig. 4). These two particular cases demonstrate the potential of SSVEPs as biomarker for covert consciousness and prognostic marker for the rehabilitation of consciousness after severe brain injuries. This potential should be further investigated in future studies with larger patient samples.

There were two other cases (P3 and P18), for whom the clinical diagnosis improved from the analysis with CRS-R on the same day to the best clinical CRS-R. In the case of P3, their revision of the initial diagnosis of coma to MCS- is based on the eye-opening at the second clinical assessment. The automatic motor response (as behavior defining MCS state) was the same in both assessments. Indeed, this patient did not show a larger response to 40 Hz visual flicker than 30 Hz stimulation, which would be expected in MCS patients. P18 showed visual pursuit and an automatic motor response, which were not present at the day of visual flicker stimulation. This revision of the diagnosis is reflected by a larger response to the 40 Hz visual flicker stimulation than to 30 Hz stimulation, as is expected for MCS patients.These cases demonstrate that the response to the visual flicker stimulation seems to be an indicator of the true state of consciousness, even though the diagnosis was different on the day of stimulation.

Although there were some changes in the clinical diagnosis from the diagnosis of the day and the best diagnosis within two weeks, the effects of the visual flicker stimulation did not change, neither for the SSVEPs nor the effect on the dominant oscillations. This stability in the main effects is surprising, taking into account that 80% of subacute DoC patients show fluctuations in the clinical signs of consciousness (Barra et al., 2025), and that the rate of misdiagnosis can be reduced from 36% to below 5% if at least five clinical assessments are done instead of a single one with the CRS-R (Wannez et al., 2017).

A significant advantage of the method we have demonstrated in the current study is the simplicity of application. The results we have presented are from a single electrode (POz), and we have deliberately not used any independent component analysis (ICA), average re-referencing or artifact correction other than the removal of the trigger artifacts caused by the visual stimulation. This means that the current method could be administered relatively easily without the need for 64 channel setups and complex analysis pipelines which might vary across working groups or require specialist training. The analysis demonstrated here could be applied with a single channel EEG amplifier and a dedicated visual stimulation device. Such a device would be relatively inexpensive and simple to use, allowing for a standardised diagnostic to be applied across clinics.

In the current study we only tested two visual flicker frequencies, 30 and 40 Hz. Our hypothesis was that SSVEPs would be larger at 40 Hz than 30 Hz for individuals who are conscious, due to resonance at 40 Hz (which has been associated with consciousness) and that this pattern would be reversed in unconscious patients. There is good reason to suppose that 40 Hz might be an index of consciousness, and 30 Hz was a reasonable control frequency as it is perceptually similar to 40 Hz flicker. Future studies should explore the use of other frequencies, as lower frequencies, e.g. 10 Hz, often show complex waveform shapes with higher harmonics in the gamma band, and this complexity might be a more suitable index of consciousness (Dowsett et al., 2020; Nuttall et al., 2022, Dowsett et al. 2026). However, choosing lower frequencies as control with regard to 40 Hz is not trivial: lower frequencies might entrain totally different frequency bands (e.g. beta band when stimulation at 25 Hz). Choosing higher frequency bands for stimulation (e.g. 35 Hz) might be perceptually too close to the target frequency at 40 Hz.. Additionally, stimulating at frequencies below 30 Hz could potentially evoke visual fatigue, migraine headache, and provoke epileptic seizures. Since the prevalence of seizures in the population of DoC patients (27%) is much higher than in the healthy population (0.76%), stimulation at frequencies lower than 30 Hz should be avoided in such a highly vulnerable patient population. Visual flicker at individualized alpha frequencies has shown increased functional connectivity across brain regions (Jaeger et al., 2023). Similarly, a study on SSVEP-based brain computer interface with healthy controls and patients with locked-in-syndrome used 10 Hz and 14 Hz visual flicker frequency and was able to demonstrate that brain responses to these two classes of stimulation were sufficiently distinct that they could be used for the classification in a command-following and communication task (Lesenfants et al., 2014). A more fine grained approach using flicker frequencies throughout the gamma band in small steps might reveal an optimal set of frequencies for indexing consciousness beyond the two we tested in the current study.

Here we used red light as this is optimal for transmission through closed eyes regarding perceived brightness (Bierman et al., 2011; Sakai, 2023). SSVEPs at 40 Hz have also been demonstrated during sleep with red light flicker built into a sleep mask (Hainke et al., 2025). However, red light flicker has also been reported to be a risk for provoking seizures, as well as stimulation at frequencies between 15 Hz and 20 Hz (Fisher et al., 2022). Future experiments might also investigate how variations in the colour or temporal properties of the flickering light affect the SSVEP, as these can be easily varied and may result in variation in the SSVEP waveform shape which is proportional to the state of consciousness.

A significant limitation of the current study is that the visual flicker device was fitted over the eyes, and it was not possible to say for sure if the DoC patients had their eyes open during the visual stimulation. This is unlikely to have affected the outcome significantly as we can assume that the majority of the patients had their eyes closed, and in the cases where they might have opened them, we expect there to be no difference in the likelihood of a DoC patient opening their eyes between 30 and 40 Hz flicker. However, future experiments should optimally use a device which can allow observation of whether the eyes are opened or closed, either by having the light source some distance away from the eyes, or by using a camera inside the eye-mounted light source. In the study by Hainke and colleagues (Hainke et al., 2025) 40 Hz visual flicker was done with much weaker light than in this study (as to not wake up participants during sleep). This implies that having a spacer between the patient's face and the goggles would not significantly diminish the brightness to levels whereSSVEPs could not be seen. Such a setup would then allow visual confirmation of whether DoC patients were opening or closing their eyes.

There is no reliable way to find out verbally if stimulation was causing any discomfort or pain, as DoC patients in coma, UWS or MCS cannot be directly asked. Although we did not see any behavioral sign of discomfort, such as flexion withdrawal or localization movement to the stimulation device, which are behavioral signs tested with the CRS-R, shortening the visual stimulation period without a significant loss of information would be advisable for future studies on SSVEP in DoC patients.

EEG was recorded from 64 electrodes, but analyses only focused on a

single occipital electrode (POz). This procedure was chosen based on previous findings (Dowsett et al., 2020) showing that capturing steady-state visual evoked potentials can be achieved with single electrodes with a high signal-to-noise ratio. The choice of a single electrode was also based on the following considerations: Firstly, the EEG caps we used for this study were saline-soaked sponges, due to the easier, faster, and pain-free application, which is important in a population of brain-injured patients. Although these electrode caps are convenient and well suited to experiments such as these, they do come with some drawbacks. One such limitation is that there is often some degree of "bridging" between electrodes, due to the cap being soaked in saline, which results in disproportionately high similarity between the signal from nearby electrodes. This issue is confounded by the fact that DoC patients are tested in a comfortable - thus supine - position, which places pressure on the occipital electrodes. As a result, we cannot rely on nearby electrodes to show the spatial variability that we would expect from conventional gel electrodes. Due to the "bridging" and the resulting smearing of spatial information, it is unlikely that an array of occipital/parietal electrodes would give a significantly better result in the current data set. Secondly, many pilot experiments with full field visual flicker have shown maximum SSVEP amplitude at Oz/POz, so it is a reasonable assumption that this electrode will be the optimal position. While this simplicity in capturing SSVEPs successfully is certainly a strength, it can also be a limitation, as the topographical distribution of SSVEPs could bear additional important information on the brain regions involved in processing visual flicker stimulation. It has been shown that occipital as well as mid-temporal regions play an important role in the generation of SSVEPs (Di Russo et al., 2007). Studying the spatio-temporal distribution of SSVEPs in DoC patients in future investigations with small arrays of gel-based electrodes spread over occipital areas could deliver precise information on the integrity of visual-perceptual processing in this vulnerable population.

Such future investigations, with significantly increased sample size, should be performed to refine the experimental design used in the present study. This would rule out the possibility of an effect of visual stimulation on SSVEPs being missed due to an underpowered study design.

In conclusion, we have demonstrated that SSVEPs in the gamma band can be evoked in all DoC patients and that the frequency specific properties of these SSVEPs are significantly different from healthy awake participants. Specifically, resonance in the 40 Hz gamma band is a promising marker of consciousness. Furthermore, we found that 40 Hz visual flicker stimulation modulates the ongoing theta oscillations in DoC patients with an average decrease in amplitude for coma/UWS patients, and an average increase for MCS/eMCS patients. Although this is a relatively small effect, we propose that this might be a potential diagnostic measure to aid in distinguishing between the two groups and further research is justified. SSVEPs are simple to record, only require a single electrode and give a very high signal-to-noise ratio without requiring complex analysis pipelines, and as such are potentially a useful tool for distinguishing states of consciousness which should be explored further.

Glossary

AD	Alzheimer's disease
CRS-R	Coma Recovery Scale-Revised
DoC	Disorders of consciousness
EEG	electroencephalography
ERP	evoked-related potential
FDG-PET	fluorodeoxyglucose-positron emission tomography fMRI = functional magnetic resonance imaging
ICA	independent component analysis
MCS	minimally conscious state
SSVEP	steady-state visual evoked potential
UWS	unresponsive wakefulness syndrome

Funding

This project is part of the multicentric application for the EU ERA-PerMed Joint Translational Call for Proposals for "Personalised Medicine: Multidisciplinary research towards implementation" (ERA PerMed JTC2019). This work was locally supported by the Federal Ministry of Education and Research (BMBF), funding code: 01KU2003.

Data availability statement

Due to the sensitive nature of the raw data gathered from patients and healthy controls, research participants were assured that raw data would remain confidential and would not be shared. Scripts that have been used during data analyses can be requested from the corresponding author upon reasonable request.

CRediT authorship contribution statement

M.J. Rosenfelder: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft. **L. Willacker:** Conceptualization, Methodology, Project administration, Validation. **T. Olander:** Data curation, Investigation. **A. Bender:** Funding acquisition, Resources, Supervision. **J. Dowsett:** Conceptualization, Formal analysis, Methodology, Software, Visualization, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2026.122069.

References

Adaikkan, C., Middleton, S.J., Marco, A., et al., 2019. Gamma entrainment binds higher-order brain regions and offers neuroprotection. Neuron 102 (5), 929–943.e8. https://doi.org/10.1016/j.neuron.2019.04.011 e8.

Arzi, A., Rozenkrantz, L., Gorodisky, L., et al., 2020. Olfactory sniffing signals consciousness in unresponsive patients with brain injuries. Nature 581 (7809), 428–433. https://doi.org/10.1038/s41586-020-2245-5.

Bareham, C.A., Roberts, N., Allanson, J., Hutchinson, P.J., Pickard, J.D., Menon, D.K., Chennu, S., 2020. Bedside EEG predicts longitudinal behavioural changes in disorders of consciousness. NeuroImage: Clin. 28, 102372.

Barra, A., Bodien, Y.G., Tan, C.O., Martens, G., Malone, C., Giacino, J.T., 2025. Behavioral fluctuation in disorders of consciousness: a retrospective analysis. Arch. Phys. Med. Rehabil. 106 (10), 1505–1513.

Bierman, A., Figueiro, M.G., Rea, M.S., 2011. Measuring and predicting eyelid spectral transmittance. J. Biomed. Opt. 16 (6), 067011. https://doi.org/10.1117/1.3593151.

Bruno, M.A., Vanhaudenhuyse, A., Thibaut, A., Moonen, G., Laureys, S., 2011. From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness. J. Neurol. 258 (7), 1373–1384. https://doi.org/10.1007/s00415-011-6114-x.

Cohen, M.X., 2017. MATLAB For Brain and Cognitive Scientists. MIT Press, Cambridge, MA.

Comanducci, A., Boly, M., Claassen, J., et al., 2020. Clinical and advanced neurophysiology in the prognostic and diagnostic evaluation of disorders of consciousness: review of an IFCN-endorsed expert group. Clin. Neurophysiol. 131 (11), 2736–2765. https://doi.org/10.1016/j.clinph.2020.07.015.

Donoghue, T., Haller, M., Peterson, E.J., Varma, P., Sebastian, P., Gao, R., Voytek, B., 2020. Parameterizing neural power spectra into periodic and aperiodic components. Nat. Neurosci. 23 (12), 1655–1665.

Dowsett, J., Herrmann, C.S., Dieterich, M., Taylor, P.C., 2020. Shift in lateralization during illusory self-motion: EEG responses to visual flicker at 10 hz and frequency-specific modulation by tACS. Eur. J. Neurosci. 51 (7), 1657–1675.

Dowsett, J., Muñoz, I.M., Taylor, P., 2026. Decoding real-world visual scenes from alpha and gamma band flicker evoked oscillations in human EEG. Sci. Rep. 16, 13221. https://doi.org/10.1038/s41598-026-42197-5.

Engemann, D.A., Raimondo, F., King, J.R., et al., 2018. Robust EEG-based cross-site and cross-protocol classification of states of consciousness. Brain 141 (11), 3179–3192. https://doi.org/10.1093/brain/awy251.

Garwood, I.C., Chakravarty, S., Donoghue, J., et al., 2021. A hidden Markov model reliably characterizes ketamine-induced spectral dynamics in macaque local field potentials and human electroencephalograms. Marinazzo D, ed. PLoS. Comput. Biol. 17 (8), e1009280. https://doi.org/10.1371/journal.pcbi.1009280.

Giacino, J.T., Ashwal, S., Childs, N., et al., 2002. The minimally conscious state: definition and diagnostic criteria. Neurology. 58 (3), 349–353. https://doi.org/10.1212/wnl.58.3.349.

Giacino, J.T., Fins, J.J., Laureys, S., Schiff, N.D., 2014. Disorders of consciousness after acquired brain injury: the state of the science. Nat. Rev. Neurol. 10 (2), 99–114. https://doi.org/10.1038/nrneurol.2013.279.

Giacino, J.T., Kalmar, K., Whyte, J., 2004. The JFK Coma Recovery Scale-revised: measurement characteristics and diagnostic utility. Arch. Phys. Med. Rehabil. 85 (12), 2020–2029. https://doi.org/10.1016/j.apmr.2004.02.033.

Graf, J., Mühlhoff, C., Doig, G.S., et al., 2008. Health care costs, long-term survival, and quality of life following intensive care unit admission after cardiac arrest. Crit. Care (Fullerton) 12 (4), R92. https://doi.org/10.1186/cc6963.

Grill, E., Klein, A.M., Howell, K., et al., 2013. Rationale and design of the prospective German registry of outcome in patients with severe disorders of consciousness after acute brain injury. Arch. Phys. Med. Rehabil. 94 (10), 1870–1876. https://doi.org/10.1016/j.apmr.2012.10.040.

He, Q., Colon-Motas, K.M., Pybus, A.F., et al., 2021. A feasibility trial of gamma sensory flicker for patients with prodromal Alzheimer's disease. Alzheimer's & Dementia: Transl. Res. Clin. Interv. 7 (1), e12178. https://doi.org/10.1002/trc2.12178.

Herrmann, C.S., 2001. Human EEG responses to 1-100Hz flicker: resonance phenomena in visual cortex and their potential correlation to cognitive phenomena. Exp. Brain Res. 137 (3–4), 346–353. https://doi.org/10.1007/s002210100682.

Iaccarino, H.F., Singer, A.C., Martorell, A.J., et al., 2016. Gamma frequency entrainment attenuates amyloid load and modifies microglia. Nature 540 (7632), 230–235. https://doi.org/10.1038/nature20587.

Kondziella, D., Bender, A., Diserens, K., et al., 2020. European Academy of Neurology guideline on the diagnosis of coma and other disorders of consciousness. Eur. J. Neurol. 27 (5), 741–756. https://doi.org/10.1111/ene.14151.

Lopez-Rolon, A., Bender, A., 2015. Hypoxia and outcome prediction in early-stage coma (Project HOPE): an observational prospective cohort study. BMC. Neurol. 15 (1), 82. https://doi.org/10.1186/s12883-015-0337-x.

Magliacano, A., Rosenfelder, M., Hieber, N., Bender, A., Estraneo, A., Trojano, L., 2021. Spontaneous eye blinking as a diagnostic marker in prolonged disorders of consciousness. Sci. Rep. 11 (1), 22393. https://doi.org/10.1038/s41598-021-01858-3.

Mainali, S., Aiyagari, V., Alexander, S., et al., 2022. Proceedings of the Second curing Coma campaign NIH Symposium: challenging the future of research for Coma and disorders of consciousness. Neurocrit. Care 37 (1), 326–350. https://doi.org/10.1007/s12028-022-01505-3.

Martorell, A.J., Paulson, A.L., Suk, H.J., et al., 2019. Multi-sensory gamma stimulation ameliorates Alzheimer's-associated pathology and improves cognition. Cell 177 (2), 256–271.e22. https://doi.org/10.1016/j.cell.2019.02.014 e22.

Owen, A.M., Coleman, M.R., Boly, M., Davis, M.H., Laureys, S., Pickard, J.D., 2006. Detecting awareness in the vegetative State. Science (1979) 313 (5792), 1402. https://doi.org/10.1126/science.1130197. –14021402-1402.

Pantev, C., Makeig, S., Hoke, M., Galambos, R., Hampson, S., Gallen, C., 1991. Human auditory evoked gamma-band magnetic fields. Proc. Natl. Acad. Sci. USA 88 (20), 8996–9000. https://doi.org/10.1073/pnas.88.20.8996.

Pastor, M.A., Artieda, J., Arbizu, J., Marti-Climent, J.M., Peñuelas, I., Masdeu, J.C., 2002. Activation of Human cerebral and cerebellar cortex by auditory stimulation at 40 hz. J. Neurosci. 22 (23), 10501–10506. https://doi.org/10.1523/JNEUROSCI.22-23-10501.2002.

Posner, M.I., Rothbart, M.K., 2007. Research on attention networks as a model for the integration of psychological science. Annu. Rev. Psychol. 58 (1), 1–23. https://doi.org/10.1146/annurev.psych.58.110405.085516.

Sahu, P.P., Tseng, P., 2023. Gamma sensory entrainment for cognitive improvement in neurodegenerative diseases: opportunities and challenges ahead. Front. Integr. Neurosci. 17, 1146687. https://doi.org/10.3389/fnint.2023.1146687.

Sakai, H., 2023. Perception of brightness when the eyes are closed. Color. Res. Appl. 48 (1), 63–68. https://doi.org/10.1002/col.22832.

Schnakers, C., Vanhaudenhuyse, A., Giacino, J., et al., 2009. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. BMC. Neurol. 9 (1), 35. https://doi.org/10.1186/1471-2377-9-35.

Singer, A.C., Martorell, A.J., Douglas, J.M., et al., 2018. Noninvasive 40-hz light flicker to recruit microglia and reduce amyloid beta load. Nat. Protoc. 13 (8), 1850–1868. https://doi.org/10.1038/s41596-018-0021-x.

Stefan, S., Schorr, B., Lopez-Rolon, A., et al., 2018. Consciousness indexing and outcome prediction with resting-State EEG in severe disorders of Consciousness. Brain Topogr. 31 (5), 848–862. https://doi.org/10.1007/s10548-018-0643-x.

Strüber, D., Herrmann, C.S., 2020. Modulation of gamma oscillations as a possible therapeutic tool for neuropsychiatric diseases: a review and perspective. Int. J. Psychophysiol. 152, 15–25. https://doi.org/10.1016/j.ijpsycho.2020.03.003.

Wannez, S., Heine, L., Thonnard, M., Gosseries, O., Laureys, S., 2017. Coma Science Group collaborators. the repetition of behavioral assessments in diagnosis of disorders of consciousness. Ann. Neurol. 81 (6), 883–889. https://doi.org/10.1002/ana.24962.

Willacker, L., Raiser, T.M., Bassi, M., et al., 2022. PerBrain: a multimodal approach to personalized tracking of evolving state-of-consciousness in brain-injured patients: protocol of an international, multicentric, observational study. BMC. Neurol. 22 (1), 468. https://doi.org/10.1186/s12883-022-02958-x.

Wislowska, M., del Giudice, R., Lechinger, J., et al., 2017. Night and day variations of sleep in patients with disorders of consciousness. Sci. Rep. 7, 266. https://doi.org/10.1038/s41598-017-00323-4.