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Psilocybin for disorders of consciousness: A case-report study

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ABSTRACT

Objective: With very few treatments available, post-comatose disorders of consciousness (DoC) pose one of the hardest challenges in modern neurology. Following promising clinical trial results in psychiatry, and a deepening understanding of their brain mechanisms, psychedelics have been suggested as a novel therapeutic drug for DoC patients, given that they increase the entropy or complexity of spontaneous activity in healthy participants. However, no attempts have been so far performed in patients with DoC.

Methods: In this case report, we describe the first-ever administration of psilocybin, a classic psychedelic (i.e., agonist at the 5-HT2A receptor), to a patient in a minimally conscious state plus. We report the behavioural effects and changes in neurophysiology measured with EEG.

Results: We report no increase in overt behavioural repertoire with validated scales, yet new spontaneous behaviour not previously seen, and increased brain complexity, as measured by the Lempel-Ziv complexity index, with changes in the underlying periodic rhythms.

Conclusions: This study contributes to future investigations exploring the use of psychedelics in DoC, enriching the discussion surrounding the role of psychedelics in medicine, and the link between brain complexity and consciousness.

Significance: This is the first-ever report of a classic psychedelic used as a treatment for post-comatose DoC.

1. Introduction

Post-comatose disorders of consciousness (DoC) are severe neurological disorders that can affect people after acquired brain damage. DoC include patients in a vegetative state/unresponsive wakefulness syndrome (VS/UWS) (Laureys et al., 2010), who can display reflexive movements yet no oriented behaviours, as well as patients in a minimally conscious state (MCS), (Giacino et al., 2002) who can demonstrate conscious behaviours, which are either language-mediated (MCS+; e.g., command-following) or not (MCS-; e.g., visual pursuit). Limited treatment options and poor prognosis underline the vital importance of research into new potential therapeutic avenues (Edlow et al., 2021; Provencio et al., 2020; Thibaut et al., 2019). Recently, psychedelics have been proposed as treatments for DoC, (Cardone et al., 2024, p. 202; Rankaduwa and Psychedelics, 2023; Scott and Carhart-Harris, 2019) given the possible link between brain complexity and consciousness (Carhart-Harris, 2018). Psychedelics can be divided into classic psychedelics acting on the serotoninergic 5-HT2A receptor, such as psilocybin, and non-classic psychedelics that mostly target other receptors, like ketamine, which is an NMDA antagonist. Extensive literature shows that psychedelics can enhance brain complexity in healthy participants (Farnes et al., 2020; Ort et al., 2023; Schartner et al., 2017; Timmermann et al., 2023). However, brain complexity is often reduced in patients with DoC (Casali et al., 2013; Casarotto et al., 2016; Sarasso et al., 2021). If a psychedelic were to increase brain complexity in people with DoC, it could theoretically enrich their phenomenal consciousness (see the entropic brain hypothesis) (Carhart-Harris, 2018) and, ideally, expand their behavioural repertoire. The entropic brain hypothesis suggests that consciousness is present within a specific range of entropy of spontaneous brain activity, and that increasing the entropy in patients

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towards this range may be beneficial. Considering both the lack of effective treatment options and the rationale of this novel treatment, investigating the potential role of psychedelics in treating patients with DoC presents huge potential benefits. While a first report using ketamine in DoC patients has recently been published (Cardone et al., 2025), so far, no research has employed a classic psychedelic as a treatment for DoC. In this paper, we present the first known case report using psilocybin, a classic psychedelic, while recording electroencephalogram in a patient suffering from DoC.

2. Methods

In this observational study, we report the case of a 41-year-old woman diagnosed with MCS+ one-year post-traumatic brain injury who received psilocybin at her home (Colorado, USA, where psilocybin is decriminalized). The patient had no significant comorbidities. Different pharmacological and brain stimulation interventions were previously tested, such as zolpidem, amantadine, ketamine, and transcranial direct current stimulation without any clinical improvement. For a longer description of the brain damage and the summary of the patient's spectrum of behaviour, please refer to the Appendix A.

The primary caregiver of the patient (husband) contacted one of the authors via email upon having read an article about the role of psychedelics as a new treatment for DoC (Gosseries and Martial, 2020). The patient was not naive to psilocybin, as she experienced it once before suffering from DoC. Before the experiment, the patient was given microdosing with psilocybin, and smaller doses of psilocybin (highest: 1.35 g). In those first sessions, some spontaneous behaviours not seen before were observed, notably the patient's right leg was raising up and the right side of the body was moving. The caregiver signed an informed consent form and the Ethics Committee document of the University of Liege in Belgium, which reviewed the case. The committee concluded that they could not offer an opinion, as this was done outside of Belgium, and in a state where psilocybin is decriminalised and accessible to the public. However, they did not object publication of the data obtained during the trial.

2.1. Timeline

On the recording day, the caregiver administered a single dose of 2.5 g liquid tincture (estimate psilocybin: 25 mg) via the gastric tube of the patient who was sitting in a reclined chair. Relaxing music from a Spotify playlist was played 12 min after intake of the substance. The favourite incense of the patient was also lit, to ensure an optimal setting. The patient was blindfolded after 20 min from intake. The blindfold was taken on and off during the experience. A medical doctor was present to ensure supervision in case of need and to record the EEG. Six behavioural evaluations were performed: the morning before the EEG, after the EEG and before psilocybin intake, an hour after psilocybin intake, before the second EEG, after the second EEG and finally approximately 4 h after intake. Additionally, pain perception during mobilisation was assessed twice. Four resting state EEGs were performed (2 pre- and 2 post-psilocybin intake), notably to ensure no abnormal activity (e.g., epilepsy) after intake. An auditory oddball paradigm was run as well, paired with EEG recording (see Appendix A). Blood pressure and heart rate were also assessed repeatedly to ensure safety. To note, effects are present from around 20 min after intake, and peak at 60–90 min after intake; the effects resolve around 5–6 h after ingestion (Hasler et al., 2004; Hasler et al., 1997). The schematic view of the timing is represented in Fig. 1.

2.2. Behavioural assessments

The level of consciousness was assessed via the Simplified Evaluation of CONsciousness Disorders SECONDs (Aubinet et al., 2020; Sanz et al., 2021), a short version of the Coma-Recovery Scale Revised (Giacino et al., 2004), typically used for the assessment of patients with a DoC, including the most relevant MCS behavioural items (Wannez et al., 2017). The SECONDs provides a number from 0 to 8, each of which has a diagnostic value (0 refers to coma, 1 to VS/UWS, etc.). A higher number represents a higher level of consciousness. To assess pain perception, the Nociceptive Coma Scale-Revised (NCS-R) was used (Chatelle et al., 2012). It evaluates motor, verbal and facial responses to pain stimulation (i.e., pressing on the finger nailbed) or care (i.e., physiotherapy or limb manipulation). It provides a number between 0 and 9, where a number higher or equal to 4 suggests potential pain perception.

All behavioural assessments were performed by the primary caregiver, who had extensively practised them in the previous months to track the evolution of his loved one. Additionally, spontaneous behaviours were also noted throughout the session.

2.3. EEG

2.3.1. Acquisition

Pre- and post-administration of psilocybin, resting state EEG was recorded with a 19-channel electrode cap WAVi™ (WAVi Research, Boulder, CO, USA) with a 250 Hz sampling rate for a total time of around 4 min in each of the 4 recordings. Electrodes were positioned in a 10–20 system (Fp1, Fp2, F3, F4, F7, F8, C3, C4, P3, P4, O1, O2, T3, T4, T5, T6, Fz, Cz, Pz) using a WAVi EEG headset with 19 WAVi eSOC™ single-use saline electrodes and two tin linked-ear reference electrodes. Before recording, impedances were set below 30 KΩ.

2.3.2. Preprocessing

The four recordings were filtered between 1–45 Hz with a Hamming window order 2000 filter (forward and backward filtering, using MATLAB's filtfilt function). The recordings were epoched into 2.5-second epochs, for a total of 98 epochs each. Channels that displayed artifacts throughout the whole recording, that prevented many otherwise good epochs from being selected, were interpolated using the default EEGLAB spherical interpolation (sccn.ucsd.edu/eeglab/). Each recording was analysed independently and then merged into the "Pre" and "Post" psilocybin administrations. Epochs presenting high levels of muscular noise were rejected. The EEG recordings were re-referenced to a common average reference. In one of the two EEG recording before psilocybin intake, two channels (C3, Pz) were interpolated, while no channel was rejected for the other recording; 88 epochs were kept out of 196 total epochs. In one of the two EEG recordings after psilocybin intake, three electrodes were interpolated (T5, T6, Pz), while no channel was rejected for the other recording; 133 epochs were kept. This resulted

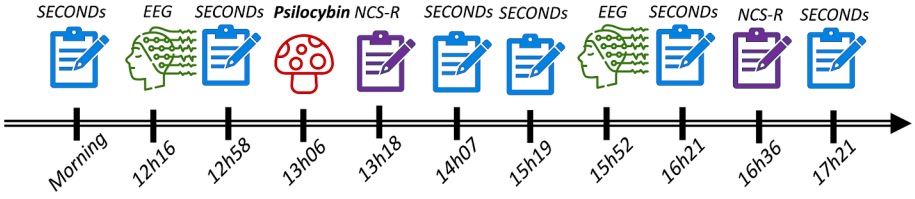

Fig. 1. Timeline of the recording day. Each EEG had two resting-states recordings and one auditory oddball paradigm. Abbreviations: SECONDs: Simplified Evaluation of Consciousness Disorders, EEG: electroencephalography, NCS-R: Nociception Coma Scale-Revised.

in 3 min and 40 s of clean data before psilocybin intake and 4 min and 42 s after the intake.

2.3.3. Lempel-Ziv complexity

The Lempel-Ziv complexity (LZC) is a measure of complexity and entropy in a symbolic sequence based on the number of distinct patterns present, and the rate at which they appear. Higher and lower LZC values are indicative of higher and lower complexity in the sequence, respectively (Abásolo et al., 2006; Schartner et al., 2015). The median of the EEG time series was used as a threshold and values over and under it were binarized to values of 1 and 0, respectively. After binarization, the LZC algorithm was applied to the epochs. For a full description of the LZC implementation used here, please refer to Abásolo et al. (2006). LZC values were normalised by the theoretical upper bound of complexity of a binary sequence ($n/log_2(n)$), where n is the number of samples in the sequence (Lempel and Ziv, 1976). LZC was computed on the pre-processed EEG time series in the 1–45 Hz frequency range, for each channel and each epoch using the median value as the threshold, and finally averaged.

2.3.4. Relative power via continuous wavelet transform

The time–frequency representation of the EEG recordings was obtained by employing the continuous wavelet transform (CWT). This technique provides a better compromise between time and frequency resolutions compared to the short-term Fourier transform, due to the shorter duration of the windows used for the spectral estimation for higher frequency bands and longer duration for lower frequency bands (Sinkkonen et al., 1995; Tallon-Baudry et al., 1996). The Morlet wavelet was used as the mother wavelet to have a biologically plausible fit for EEG signals (Roach and Mathalon, 2008).

Relative power (RP) is a measure that describes the spectral contents of a signal by indicating how each frequency band of the power spectrum contributes to its total power. The RP can be obtained from a wavelet scalogram (absolute value of the CWT squared) by summing its components belonging to the frequency range of each specific band, with previous normalisation of the scalogram in the range of bands in question. In this case, the scalogram was normalised in the 1–45 Hz range before RP computation (Núñez et al., 2017). We extracted the power of the following bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta-1 (13–19 Hz), beta-2 (19–30 Hz) and gamma (30–45 Hz). Relative power in each band was computed by dividing the power in that band by the power over all frequency bands. In addition, the absolute power was also computed for all frequency bands.

2.3.5. Functional connectivity

Two measures of functional connectivity were calculated in the study. To account for both amplitude and phase connectivity of the recordings, the amplitude envelope correlation (AEC) and phase-locking value (PLV) were computed. The time series were pairwise orthogonalized for each time-window separately before computing both measures to minimise the effects of leakage between sources, which can give rise to erroneous correlations (Brookes et al., 2012). Moreover, the signal was filtered in the frequency bands of interest before computation.

The amplitude envelope correlation (AEC) is a simple but robust method of detecting amplitude-based connectivity, which consists of measuring the correlation between the envelopes of filtered time series (Colclough et al., 2016). The power envelope of the signal is derived from the absolute value of the analytic signal, obtained with the Hilbert transform. Then, the Pearson correlation of the envelopes is computed to obtain the functional connectivity (Liu et al., 2010).

The phase-locking value (PLV) measures the phase synchrony between two time-series by looking for latencies that are temporally stable ("phase locking") between the instantaneous phases of two signals (Lachaux et al., 1999). To compute the PLV, the instantaneous phase must be estimated via the Hilbert transform. Afterwards, the inter-trial variability of the phase difference is obtained, where the higher the variability, the lower the PLV (Lachaux et al., 1999). The measure can be extended to the resting state by assessing the phase difference over time instead of over trials, which is the implementation we used in this study. (Bruña et al., 2018).

2.3.6. Statistical modelling

For LZC, we averaged over epochs and applied a paired t-test over electrodes between sessions to assess the effect of psilocybin. Additionally, we used a repeated-measures ANOVA with the Greenhouse-Geisser correction to test the changes in power and connectivity. We corrected the results with Bonferroni correction, assuming 4 different tests for EEG (complexity, power, amplitude-based and phase-based connectivity), thus considering a critical alpha of 0.0125 (0.05/4). Apart from complexity, we further corrected for the 6 bands considered, with a critical p-value of 0.002 (0.0125/6).

3. Results

3.1. Behavioural results

3.1.1. SECONDs and NCS-R

At the start of the recording day, the patient was diagnosed MCS- (visual pursuit: score of 4). In the following SECONDs before the first EEG session, the patient was considered MCS+ (reproducible response to command and visual pursuit: score of 6). She was able to respond to the command "Look up". She opened the right eye and the mouth with no additional movement. Between the psilocybin administration and the post-EEG measurements, the patient was diagnosed with UWS (eyes opened: score of 1) in both SECONDs. After the post-EEG, both SECONDs were scored as MCS- with visual pursuit (score of 4). For a visual representation, see Fig. 2.

An NCS-R was recorded at 13h18 (+12 min after psilocybin intake; no effects expected yet) during mobilisation where flexion withdrawal and grimaces were observed (score of 4). Another NCS-R was reported at 16h36 (+3h30 after psilocybin intake) during the mobilisation from the reclined chair to the bed, and no response was observed (score of 0).

3.1.2. Spontaneous behaviours and other observations

While there was no clinical diagnosis improvement as determined by the SECONDs, some spontaneous behaviours emerged that were never exhibited at rest without psilocybin. In particular, the patient lifted both legs, which remained up. Her left leg had already displayed such movement, but not her right one. Additionally, her right leg was shivering quickly. She had both her eyes and mouth wide open, which

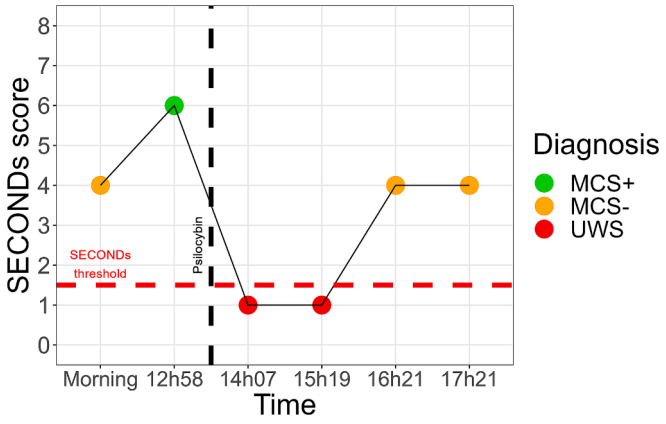

Fig. 2. Behavioural results with the SECONDs. SECONDs total scores during the day of the psilocybin intake. The horizontal red line represents the cutoff of the SECONDs score for the presence of consciousness (at least a score of 2). The vertical black line represents the intake of psilocybin (13h06).

according to her caregiver had not been seen before without psilocybin (but had been seen with the prior lower doses, with less intensity).

An increase in blood pressure was observed around 14h32 (158/82; HR: 83 bpm), which led to the administration of CoQ10 and NSE cysteine at 15h00 to control it. At 15h07, the blood pressure was 138/100 (HR: 79 bpm). No other adverse effects were observed (i.e., no severe increase of heart rate). See Appendix A (Supp. Fig.1) for the values of blood pressure and heart rate.

3.2. EEG results

The EEG showed a marked change after the intake of psilocybin, that could be observed already with the visualization of the preprocessed data. See Appendix A (Supp. Fig. 2) for a visual display of the EEG data from the two sessions per condition (pre- and post-psilocybin). EEG results showed a distinct change following psilocybin intake. For a visual representation of the EEG results, please consult Fig. 3. We observed a general increase in whole-brain entropy/complexity (LZC) after psilocybin intake ($t_{18} = 6.64$, p-value < 0.0001; mean (sd): Pre: 0.30 (0.05); Post: 0.47 (0.09)). We also observed a change in the relative power spectrum following psilocybin administration (Band: $F_{1.14,\ 20.57} = 262.82$, p-value < 0.0001; Session: $F_{1,\ 18} = 35.82$, p-value < 0.0001; Band*Session: $F_{1.11,\ 20.05} = 36.41$, p-value < 0.0001). In particular, there was a decrease in slow oscillations (e.g., delta), and an increase in higher frequency (e.g., gamma), that underlies this significant interaction effect. This was evident at the level of relative power (frequency band: [$mean_{pre}$ (sd_{pre}) − $mean_{post}$ (sd_{post})]; delta [0.42 (0.05) − 0.31 (0.07)], theta [0.18 (0.01) − 0.15 (0.02)], alpha [0.15 (0.02) − 0.14 (0.01)], beta1 [0.11 (0.01) − 0.13 (0.01)], beta2 [0.12 (0.02) − 0.18 (0.03)], and gamma: [0.21 (0.03) − 0.34 (0.07)]). We could also see a relevant change in both amplitude- (AEC; Band: $F_{3.46,\ 588.23} = 5128.08$, p-value < 0.0001; Session: $F_{1,\ 170} = 135.39$, p-value < 0.0001; Band*Session: $F_{3.26,\ 554.32} = 69.03$, p-value < 0.0001) and phase-based connectivity (PLV; Band: $F_{2.93,\ 498.27} = 4456.34$, p-value < 0.0001; Session: $F_{1,\ 170} = 49.29$, p-value < 0.0001; Band*Session: $F_{3.06,\ 519.36} = 24.72$, p-value < 0.0001). We observed a higher connectivity in the delta frequency band after psilocybin administration, as measured by AEC, but a lower functional connectivity in all other frequency bands. PLV showed a less clear picture, demonstrating a decrease in strength, especially at higher frequencies (i.e., Beta-2 and Gamma). Post-hoc comparisons between different bands for each measurement are presented in the Appendix A (Supp. Table 1). The EEG showed no sign of seizure at any point. Consult the Appendix A for a representation of the power spectrum and absolute power (Supp. Fig. 3), and for the results of the auditory oddball paradigm (Supp. Fig. 4).

4. Discussion

In this observational case study, we have reported the first-ever known administration of psilocybin to a patient with DoC. No amelioration of her clinical diagnosis was noted, but there was a marked change in spontaneous behaviours and the neurophysiological markers captured by EEG.

After the administration of the drug, the patient was unresponsive for the first two SECONDs assessments (the second one performed at +2h30 from drug administration). One possibility that could explain the unresponsiveness, is that psilocybin might have pushed the patient into a UWS state. At the moment of writing this report, there is no reason to think that a patient who is MCS (i.e., conscious) would become UWS (i.e., unconscious) due to psilocybin. If that was the case, psilocybin would act in DoC as an anaesthetic which, given the information we have, is extremely unlikely. While behaviourally unresponsive, it is more probable that the patient was just disconnected from the environment, meaning that there was an internal experience, but it was detached from the world or unable to interact with it. In other words, even if unable to respond to commands as per the SECONDs, the patient might have had an altered internal awareness (see also Cardone et al., 2024 for a longer discussion). This is however currently impossible to verify given that she appeared unconscious according to the standard assessments. Our observations and resulting hypotheses motivate us to reconsider the assessment of conscious behaviours in such cases. Specifically, we speculate that assessing spontaneous as opposed to cued behaviour may improve the sensitivity of detecting alterations of conscious experience in DoC patients (Mat et al., 2022). While we considered here resting state EEG, two recent human imaging studies found that psychedelics have a massive effect on spontaneous brain activity that is otherwise subdued by task conditions and external stimulation (Mediano et al., 2024; Siegel et al., 2024).

New signs of consciousness currently investigated in DoC include spontaneous behaviours (e.g., spontaneous eye blink rate) (Magliacano et al., 2021), non-brain physiological data (e.g., electrocardiogram (Rosas et al., 2023), and respiration patterns (Arzi et al., 2020)), which are easy to record without heavily interfering with the person undergoing a psychedelic experience. We should note that the patient displayed spontaneous lifting of both legs; while she had lifted her left leg before, she had never lifted the right one without psilocybin. In other words, it is possible that the patient was having a rich experience, in line with the increased EEG complexity and the 'entropic brain hypothesis' (Carhart-Harris, 2018) without being able to respond to the environment. In the first SECONDs, one hour after the administration of psilocybin, corresponding to the rising phase of the subjective experience in healthy volunteers (Hasler et al., 2004), the patient was unresponsive. Only in the SECONDs, done at +3h15 and +4h15 from intake, the patient was able to display visual pursuit, but not respond to commands as on other occasions.

Regarding pain during mobilisation, the NCS-R scores suggest potential pain perception before psilocybin (score of 4) while no pain perception was observed after psilocybin intake (score of 0). This finding is consistent with prior studies that have reported that psychedelics may have the potential to alleviate pain symptoms in a multitude of conditions (e.g., phantom limbs, cluster headache, cancer pain, spinal cord injury) (Goel et al., 2023; Robinson et al., 2024; Van Der Walt and Parker, 2023).

Throughout the experiment, the caregiver removed and repositioned the blindfold when considered beneficial to her (e.g., taking off the blindfold when the blood pressure increased to help her reconnect with the physical environment – as per 'grounding' (Siegel et al., 2024)). The increase in blood pressure was an adverse effect that required medical attention. It is worth noticing that the increase was within the reported range in healthy participants under psilocybin, and is consistent with changes seen in other trials with patients having emotionally relevant experiences during psychedelics (Wsół, 2023). In fact, in a previous report, up to a third of participants had systolic blood pressure higher than 160 (Griffiths et al., 2016). While difficult to pinpoint, possible reasons for the high blood pressure might be linked to individual sensitivity to the substance, the potentially very emotionally valence of the experience, and possibly DoC-specific features that played a role (e.g., lower cardiovascular fitness). Whether the reduction of blood pressure following blindfolding suggests that there was environmental awareness, is a question that remains open. We should note that the behavioural changes partially overlap with the clinical signs of a serotoninergic syndrome. Specifically, the increase in heart rate and blood pressure, as well as the muscle twitching and shivering, are symptoms of serotoninergic syndrome. Nevertheless, both heart rate and blood pressure decreased with contextual manipulation, such as taking off the blindfold, which would not be the case for a serotoninergic syndrome. In other words, while it is possible to ease some physiological changes caused by the psychedelic experience through "grounding" (Siegel et al., 2024), it is not possible to do so with a serotoninergic syndrome. Even if we do not consider having assisted to a serotoninergic syndrome in this case, future investigations should be mindful of the possibility of those when treating heavily medicated patients.

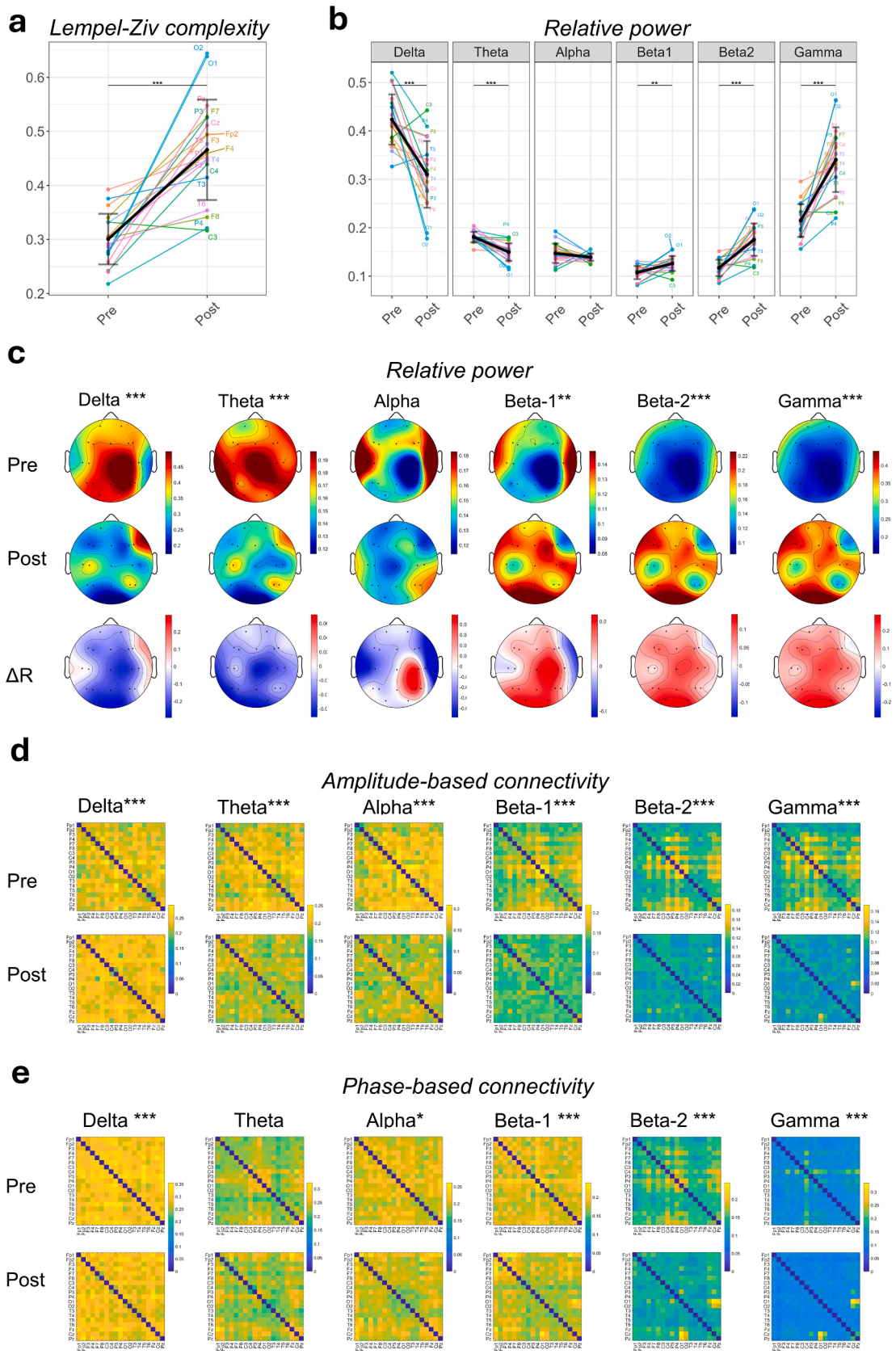

Fig. 3. Resting state EEG results. Complexity (a) as a function of electrodes. In black, mean values with standard deviations. Relative power (b) for each power band before and after drug administration as a function of electrodes. In black, mean values with standard deviations. Topographic plots (c) of the average relative power at each electrode location for each session and frequency band. Below, the difference between Post and Pre. Average amplitude envelope correlation values (d) for each session and frequency band. Average phase locking values (e) for each session and frequency band. Legend: *p-value < 0.01; **p-value < 0.001; ***p-value < 0.0001.

On the neurophysiological side, we observed some features that are characteristic of psychedelic administration in healthy participants (i.e., increased whole-brain LZC) (Farnes et al., 2020; Ort et al., 2023; Schartner et al., 2017; Timmermann et al., 2023), and others that were not (e.g., there was no change in alpha power) (Kometer et al., 2015; Schenberg et al., 2015; Timmermann et al., 2023; Timmermann et al., 2019). The increase in LZC would suggest a richer subjective experience following psilocybin – as per the entropic brain hypothesis (Carhart-Harris, 2018). In contrast to previous investigations using psychedelics (Timmermann et al., 2023), we did not observe a significant decrease of alpha power following the intake of psilocybin. One possible explanation is that patients with DoC do not show a prominent alpha rhythm at baseline, thus possibly obscuring the effect of psilocybin on this specific band. Nevertheless, we could appreciate a general increase of higher frequencies and a decrease of slower ones, which is linked with the increment of LZC (Medel et al., 2023). While we expected a higher state of consciousness, which would have resulted in a more varied behavioural repertoire, our findings do not disprove the hypothesis that brain complexity and consciousness are tightly linked. As discussed above, there is the possibility that psilocybin induced a state of disconnected consciousness, rather than unconsciousness. Had we observed richer behaviour with no substantial change in brain complexity, this would have falsified our hypothesis. We should highlight that previous investigations in rats have reported independence between markers of complexity of spontaneous EEG and behaviour with an anaesthesia paradigm (Pal et al., 2020; Pal et al., 2018). Similarly, other experiments with rats have shown the importance of brain complexity measured with a perturbation to dissociate conscious states and (un)responsiveness (Arena et al., 2022; Arena et al., 2021). Future investigation should better explore which indexes ultimately dissociate consciousness and responsiveness. For a discussion about the merits and the limits of spontaneous EEG complexity indexes compared to other proxies, we refer to the literature (Cardone et al., 2024; Sarasso et al., 2021). Brain connectivity changed as well, showing a weaker connectivity in both amplitude-based and phase-based measures for most of the bands. This was particularly evident with the amplitude-based connectivity. This aligns with previous findings that suggest a decrease in connectivity in human EEG (Tylš et al., 2014) and animal neurophysiology (Vejmola et al., 2021) after psilocybin intake. It can in theory be caused by the desynchronisation that has been described in the psychedelic state (Muthukumaraswamy et al., 2013). Furthermore, it is possible that some changes in power might have driven the effects on connectivity (see for an example between AEC and amplitude of oscillations (Tewarie et al., 2019)). Nevertheless, while the phenomenon described is the same, i.e., underlying neural oscillations, providing multiple descriptors can provide additional relevant information. For example, we observed that most of the connectivity measured significantly decreased (except AEC in delta), even if we could see a change in the power spectrum (e.g., lower delta, higher gamma).

Several limitations to this report should be acknowledged. First, this is a single case report. Future investigations should include more patients, as it is known that treatment efficacy is low in patients with DoC (Thibaut et al., 2019). Some treatments such as zolpidem work in only 5 % of the DoC population (Whyte et al., 2014), while others like transcranial direct current stimulation have shown better results in subgroups of the DoC population. (Thibaut et al., 2017). Second, the drug administration was not blind and there was no placebo condition. These two limits would have been overcome by a randomised clinical trial. Third, while we observe limited changes at the level of movement (e.g., lifting both legs), we cannot exclude micromovements and/or muscular tension that could have partially caused the increase power in gamma frequency. Nevertheless, at the stage of preprocessing, the EEG session post-psilocybin intake was in fact the cleanest one, as indicated by the highest number of epochs maintained, which suggests that the level of muscle contamination was minimal. Fourth, the patient was observed only on one occasion using a moderate/high dose of psilocybin. The dose can be considered "standard" recreational use (MacCallum et al., 2022) and the corresponding psilocybin dose (MacCallum et al., 2022) has been used in previous investigations for healthy participants (Siegel et al., 2024) and in clinical trials (Carhart-Harris et al., 2021, 2016; Goodwin et al., 2022; Raison et al., 2023). Note that while no positive effects had been observed for this particular patient at lower doses, new studies should explore the optimal dosage for therapeutic aims. As this was an observational study, the authors had no role in deciding the dose that was given. Understanding whether there is an optimal dose (whether higher or lower), is of critical importance. Increasing the number of drug administrations might also be more effective, particularly in relation to potential sustained effects. The patient reported here had been administered smaller doses in the previous weeks. It is possible these might have resulted in a habituation effect. Nevertheless, the degree of such phenomenon is not quantifiable with the current knowledge. Neurorehabilitation procedures might as well be considered in the intervals between doses. Fifth, while music was played during the psychedelic experience as recommended for an optimal setting (Eisner, 1997), it was unfortunately not done prior its administration. Listening to music has been described to influence the psychedelic experience (Barrett et al., 2018; Barrett et al., 2017), and it has been recently shown to induce specific changes in fMRI connectivity (Kaelen et al., 2016), dynamics (Adamska and Finc, 2023), and response to in-silico perturbation (Jobst et al., 2021) after LSD intake. Whether music might have induced an increase in EEG complexity per se, independent from the drug, is unknown. Future investigation should use homogenous setting before and after substance intake. Sixth, patients with DoC fluctuate heavily across and between days, as evidenced by fluctuation of diagnosis before the psilocybin intake. Thus, response to the drug might be state-dependent. In the current study, the patient was MCS+ before psilocybin administration, which is the best diagnosis possible for this case. Whether we might have had different results if the baseline condition was VS/UWS, is unknown. It would be beneficial to understand whether psilocybin can promote a completely new and distinct global state from the one that the patient would spontaneously show over time, or if it was closer to one normally inhabited. On the same lines, additional EEG recordings to characterize spontaneous fluctuations would have benefited the description of this case. Prospective studies should implement longitudinal (neurophysiological) recordings to characterize fluctuations to further understand DoC neurophysiology and treatment response. Finally, given the observational nature of this report, we did not have the possibility to implement a high-density EEG with gel-based electrodes. Future investigation, especially if performed within a clinical trial, should consider using a set-up with a higher spatial resolution and/or gel-based electrodes, possibly recording longer portions of the experiment and optimally throughout the whole psychedelic experience. In this case, multiple EEG recordings of about 4 min maximized the possibility to capture brain signals in this challenging clinical context. These recording lengths, while short at first glance, are often used in the literature (see for example Annen et al., 2023 where 5 min of clean data were employed).

While we have here reported the effect of one typical psychedelic, little is known about the effect of atypical ones that are either legal (i.e., ketamine) (Krystal et al., 2019; Vlisides et al., 2018) or are close to legalisation for specific use cases (i.e., MDMA) (Danforth et al., 2018; Mitchell et al., 2021). Although there is data on the effect of ketamine on LZC on EEG data, (Farnes et al., 2020; Li et al., 2022) there is none for MDMA. Even less information is available about putative non-psychedelic analogues that are looked upon as potentially useful adjuncts to the current therapeutic options (Cameron et al., 2021; Lewis et al., 2023; Lu et al., 2021). Furthermore, given the neuroplastic effects of psychedelics (Aleksandrova and Phillips, 2021; Ly et al., 2018; Vargas et al., 2023), it is possible that even if they might not acutely elevate measurable improvements in the level of consciousness, they might have a sub-acute neuroplastic action that could facilitate rehabilitation, similarly to coadjuvant drugs. In this regard, the timing of both dosing

and following rehabilitation is of cogent importance. Future investigations should investigate if there is any relevant and beneficial neuroplastic effect in these patients.

Our study is the first using psilocybin, a classic psychedelic, to potentially treat patients with DoC. While we did not observe improvements in overt conscious behaviour using standardised tests, we did observe novel spontaneous behaviours not seen before. Moreover, we observed changes in neurophysiology associated with enrichment of phenomenal experience by other psychedelic studies (Timmermann et al., 2023), with no severe adverse effects. This study opens the door for future research into the use of classic psychedelics for DoC patients, for whom only modelling work has been proposed so far (Alnagger et al., 2024). As with the rest of clinical research, additional preclinical animal work would benefit from building up fundamental knowledge on the causes and possible treatment for DoC (van der Lande et al., 2023). Nevertheless, compared to other (neurological) conditions with trackable biomarkers, consciousness relies heavily on language, which is currently a limiting factor for animal models of DoC. Thus, provided it is safe, we deem critical to have controlled and coordinated randomized clinical trials, as more fundamental research might have roadblocks caused by the first-person nature of the object of study. While observational studies are valuable starting points, we stress the importance of having controlled medical trials in research centres and hospitals. The feasibility of such study strongly depends on the evolution of the legal status of this substance. While it varies from country to country, there are different formulations of psilocybin that are currently available in some countries in Europe and North America. Possibility to access the substance strongly limits the extent of possible countries participating in a potential clinical trial. Nevertheless, we believe this might be beneficial for updating the regulation for research in other countries as well, which might be more restrictive at the moment. Even if such experimentations have raised several ethical questions (Peterson et al., 2019), assuming a supporting experimental setting (Rankaduwa and Psychedelics, 2023) and considering the safety profile (Nutt et al., 2010), controlled clinical trials are the optimal way to provide experimental control for these experiments. While we refer to the past literature for a more in-detail account and discussion on the subject (Cardone et al., 2024; Peterson et al., 2019; Rankaduwa and Psychedelics, 2023; Scott and Carhart-Harris, 2019), it is important to touch upon the topic of ethics in this first report. In particular, it is relevant to dive into the point of contention of whether giving a medication to a person who cannot consent, which is one of the most common concerns in such interventions. While it is true this posits a serious ethical question, any medication or medical attention given to the individual with DoC is done so without their explicit consent. As other cases of people who cannot consent, this authority is delegated to their legal representative. This is to say, that problem of consent is a common issue with DoC patients, and is not specific of psychedelics *per se*. As said, while psychedelics lead to profoundly important experiences, the chance of having challenging ones is contained by optimally prepare the setting of the protocol (Rankaduwa and Psychedelics, 2023). So, we do not consider this problem uniquely cogent to this treatment. It should also be noted that we discourage self-medication in the absence of medical advice for any drug or medical procedure. This is especially important for psychedelics given the media attention they receive, the relative ease of acquisition compared with other drugs and devices (e.g., amantadine, transcranial magnetic stimulation), their illegality in most jurisdictions, and the relatively low associated physical risk. Future investigations should expand this case report to thoroughly investigate the effectiveness of psychedelics in patients with DoC.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2025.02.264.

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